

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

REQUEST FOR FILING NATIONAL PHASE OF

PCT APPLICATION UNDER 35 U.S.C. 371 AND 37 CFR 1.494 OR 1.495

To: Hon. Commissioner of Patents  
Washington, D.C. 20231

00909

TRANSMITTAL LETTER TO THE UNITED STATES  
DESIGNATED/ELECTED OFFICE (DO/EO/US)Atty Dkt: P 0281467 /Z 70470/UST  
M# /Client Ref.

From: Pillsbury Winthrop LLP, IP Group:

Date: July 18, 2001

This is a **REQUEST** for **FILING** a PCT/USA National Phase Application based on:

1. International Application <u>PCT/GB00/00284</u> <sup>↑ country code</sup>	2. International Filing Date 1      January      2000 Day      MONTH      Year	3. Earliest Priority Date Claimed 5      February      1999 Day      MONTH      Year (use item 2 if no earlier priority)
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4. Measured from the earliest priority date in item 3, this PCT/USA National Phase Application Request is being filed within:

(a)  20 months from above item 3 date      (b)  30 months from above item 3 date,  
(c) Therefore, the due date (unextendable) is August 5, 2001

Title of Invention CHEMICAL COMPOUNDSInventor(s) FAULL, Alan Wellington et al

Applicant herewith submits the following under 35 U.S.C. 371 to effect filing:

Please immediately start national examination procedures (35 U.S.C. 371 (f)).  
 **A copy of the International Application** as filed (35 U.S.C. 371(c)(2)) is transmitted herewith (file if in English but, if in foreign language, file only if not transmitted to PTO by the International Bureau) including:  
a.  Request;  
b.  Abstract;  
c. 70 pgs. Spec. and Claims;  
d.        sheet(s) Drawing which are  informal  formal of size  A4  11"

9.  **A copy of the International Application has been transmitted by the International Bureau.**

10. **A translation of the International Application** into English (35 U.S.C. 371(c)(2))

a.  is transmitted herewith including: (1)  Request; (2)  Abstract;  
(3)        pgs. Spec. and Claims;  
(4)        sheet(s) Drawing which are:  
 informal  formal of size  A4  11"  
b.  is not required, as the application was filed in English.  
c.  is not herewith, but will be filed when required by the forthcoming PTO Missing Requirements  
Notice per Rule 494(c) if box 4(a) is X'd or Rule 495(c) if box 4(b) is X'd.  
d.  Translation verification attached (not required now).

09/889516

JCT3 Rec'd PCT/PTO 18 JUL 2001

11.  Please see the attached Preliminary Amendment

12.  Amendments to the claims of the International Application **under PCT Article 19 (35 U.S.C. 371(c)(3))**, i.e., **before 18th month from first priority date above in item 3, are transmitted herewith (file only if in English) including:**

13.  PCT Article 19 claim amendments (if any) have been transmitted by the International Bureau

14.  Translation of the amendments to the claims **under PCT Article 19 (35 U.S.C. 371(c)(3))**, i.e., **of claim amendments made before 18th month, is attached (required by 20th month from the date in item 3 if box 4(a) above is X'd, or 30th month if box 4(b) is X'd, or else amendments will be considered canceled).**

15. **A declaration of the inventor (35 U.S.C. 371(c)(4))**

a.  is submitted herewith  Original  Facsimile/Copy

b.  is not herewith, but will be filed when required by the forthcoming PTO Missing Requirements Notice per Rule 494(c) if box 4(a) is X'd or Rule 495(c) if box 4(b) is X'd.

16. **An International Search Report (ISR):**

a. Was prepared by  European Patent Office  Japanese Patent Office  Other

b.  has been transmitted by the international Bureau to PTO.

c.  copy herewith (2 pg(s).)  plus Annex of family members (1 pg(s).).

17. **International Preliminary Examination Report (IPER):**

a.  has been transmitted (if this letter is filed after 28 months from date in item 3) in English by the International Bureau with Annexes (if any) in original language.

b.  copy herewith in English.

c. 1  IPER Annex(es) in original language ("Annexes" are amendments made to claims/spec/drawings during Examination) including attached amended:

c. 2  Specification/claim pages # \_\_\_\_\_ claims # \_\_\_\_\_  
Dwg Sheets # \_\_\_\_\_

d.  Translation of Annex(es) to IPER **(required by 30<sup>th</sup> month due date, or else annexed amendments will be considered canceled).**

18. **Information Disclosure Statement** including:

a.  Attached Form PTO-1449 listing documents

b.  Attached copies of documents listed on Form PTO-1449

c.  A concise explanation of relevance of ISR references is given in the ISR.

19.  **Assignment** document and Cover Sheet for recording are attached. Please mail the recorded assignment document back to the person whose signature, name and address appear at the end of this letter.

20.  Copy of Power to IA agent.

21.  **Drawings** (complete only if 8d or 10a(4) not completed): \_\_\_\_\_ sheet(s) per set:  1 set informal;  
 Formal of size  A4  11"

22. Small Entity Status  is **Not** claimed  is claimed (**pre-filing confirmation required**)

22(a) \_\_\_\_\_ (No.) Small Entity Statement(s) enclosed (since 9/8/00 Small Entity Statements(s) not essential to make claim)

23. **Priority** is hereby claimed under 35 U.S.C. 119/365 based on the priority claim and the certified copy, both filed in the International Application during the international stage based on the filing in (country) **GREAT BRITAIN** of:

Application No.	Filing Date	Application No.	Filing Date
(1) 9902455.6	February 5, 1999	(2) _____	_____
(3) _____	_____	(4) _____	_____
(5) _____	_____	(6) _____	_____

a.  See Form PCT/IB/304 sent to US/DO with copy of priority documents. If copy has not been received, please proceed promptly to obtain same from the IB.

b.  Copy of Form PCT/IB/304 attached.

24. Attached: 2 copies of Form PCT/IB/306

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JC18 Rec'd PCT/PTO 18 JUL 2001

25 Per Item 17.c2, cancel original pages # \_\_\_\_\_, claims # \_\_\_\_\_, Drawing Sheets # \_\_\_\_\_26. **Calculation of the U.S. National Fee (35 U.S.C. 371 (c)(1)) and other fees is as follows:**Based on amended claim(s) per above item(s)  12,  14,  17,  25 (hilite)

Total Effective Claims	minus 20 =	x \$18/\$9 = \$0	966/967
Independent Claims	minus 3 =	x \$80/\$40 = \$0	964/965
If any proper (ignore improper) Multiple Dependent claim is present,		add\$270/\$135 +0	968/969

## BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(4)): ➔ ➔ BASIC FEE REQUIRED, NOW ➔ ➔ ➔ ➔

A. If country code letters in item 1 are not "US", "BR", "BB", "TT", "MX", "IL", "NZ", "IN" or "ZA"

See item 16 re:

1. Search Report was <u>not</u> prepared by EPO or JPO -----	x add\$1000/\$500	960/961
2. Search Report was prepared by EPO or JPO -----	x add\$860/\$430 +860	970/971

SKIP B, C, D AND E UNLESS country code letters in item 1 are "US", "BR", "BB", "TT", "MX", "IL", "NZ", "IN" or "ZA"

→ <input type="checkbox"/> B. If <u>USPTO</u> did not issue <u>both</u> International Search Report (ISR) and (if box 4(b) above is X'd) the International Examination Report (IPER), -----	x add\$1000/\$500 +0	960/961
→ <input type="checkbox"/> C. If <u>USPTO</u> issued ISR but not IPER (or box 4(a) above is X'd), -----	x add\$710/\$355 +0	958/959
→ <input type="checkbox"/> D. If <u>USPTO</u> issued IPER but IPER Sec. V boxes <u>not all</u> 3 YES, -----	x add\$690/\$345 +0	956/957
→ <input type="checkbox"/> E. If international preliminary examination fee was paid to <u>USPTO and Rules 492(a)(4) and 496(b) satisfied</u> (IPER Sec. V <u>all</u> 3 boxes YES for <u>all</u> claims), -----	x add \$100/\$50 +0	962/963

**SUBTOTAL = \$860**

28. If Assignment box 19 above is X'd, add Assignment Recording fee of ---\$40	+0	(581)
29. Attached is a check to cover the -----	<b>TOTAL FEES</b>	<b>\$860</b>

Our Deposit Account No. 03-3975

Our Order No. 009901 | 0281467



009909

**CHARGE STATEMENT:** The Commissioner is hereby authorized to charge any fee specifically authorized hereafter, or any missing or insufficient fee(s) filed, or asserted to be filed, or which should have been filed herewith or concerning any paper filed hereafter, and which may be required under Rules 16-18 and 492 (missing or insufficient fee only) now or hereafter relative to this application and the resulting Official document under Rule 20, or credit any overpayment, to our Account/Order Nos. shown above for which purpose a duplicate copy of this sheet is attached.

This **CHARGE STATEMENT** does not authorize charge of the issue fee until/unless an issue fee transmittal form is filed

**Pillsbury Winthrop LLP**  
**Intellectual Property Group**

By Atty: Donald J. Bird

Reg. No. 25323

Sig:

Fax: (703) 905-2500  
Tel: (703) 905-2018

Atty/Sec: DJB/mhn

NOTE: File in duplicate with 2 postcard receipts (PAT-103) & attachments.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION OF

Inventor(s): FAULL, Alan W. et al

Filed: Herewith

Title: CHEMICAL COMPOUNDS

July 18, 2001

PRELIMINARY AMENDMENT

Hon. Commissioner of Patents  
Washington, D.C. 20231

Sir:

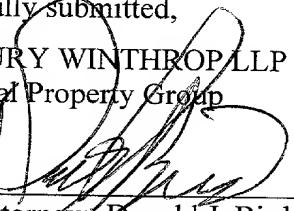
Please amend this application as follows:

IN THE SPECIFICATION:

At the top of the first page, just under the title, insert

--This application is the National Phase of International Application  
PCT/GB00/00284 filed January 31, 2000 which designated the U.S.  
and that International Application  
 was       was not published under PCT Article 21(2) in English...

Respectfully submitted,  
PILLSBURY WINTHROP LLP  
Intellectual Property Group

By: 

Attorney: Donald J. Bird  
Reg. No: 25323  
Tel. No.: (703) 905-2018  
Fax No.: (703) 905-2500

Atty\Sec. DJB/mhn  
1600 Tysons Boulevard

McLean, VA 22102  
(703) 905-2000

CHEMICAL COMPOUNDS

The present invention relates to chemical compounds, to their production as well as to pharmaceutical compositions containing them as well as to their use in therapy, in particular 5 of inflammatory disease.

MCP-1 is a member of the chemokine family of pro-inflammatory cytokines which mediate leukocyte chemotaxis and activation. MCP-1 is a C-C chemokine which is one of the most potent and selective T-cell and monocyte chemoattractant and activating agents known. MCP-1 has been implicated in the pathophysiology of a large number of inflammatory 10 diseases including rheumatoid arthritis, glomerular nephritides, lung fibrosis, restenosis (International Patent Application WO 94/09128), alveolitis (Jones et al., 1992, *J. Immunol.*, 149, 2147) and asthma. Other disease areas where MCP-1 is thought to play a part in their pathology are atherosclerosis (e.g. Koch et al., 1992, *J. Clin. Invest.*, 90, 772 -779), psoriasis (Deleuran et al., 1996, *J. Dermatological Science*, 13, 228-236), delayed-type 15 hypersensitivity reactions of the skin, inflammatory bowel disease (Grimm et al., 1996, *J. Leukocyte Biol.*, 59, 804-812), multiple sclerosis and brain trauma (Berman et al, 1996, *J. Immunol.*, 156, 3017-3023). An MCP-1 inhibitor may also be useful to treat stroke, reperfusion injury, ischemia, myocardial infarction and transplant rejection.

MCP-1 acts through the MCP-1 receptor (also known as the CCR2 receptor). MCP-2 20 and MCP-3 may also act, at least in part, through the MCP-1 receptor. Therefore in this specification, when reference is made to "inhibition or antagonism of MCP-1" or "MCP-1 mediated effects" this includes inhibition or antagonism of MCP-2 and/or MCP-3 mediated effects when MCP-2 and/or MCP-3 are acting through the MCP-1 receptor.

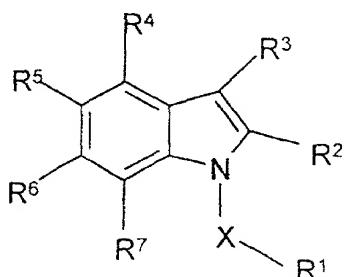
Copending International Patent Application Nos. PCT/GB98/02340 and 25 PCT/GB98/02341 describe and claim groups of compounds based upon the indole ring structure which are inhibitors of MCP-1 and therefore have applications in therapy.

The use of certain indole derivatives as NMDA antagonists is described in USP5051442, WO9312780, EP-483881. Other indoles and their use as inhibitors of leukotriene biosynthesis is described in for example, EP-A- 275-667.

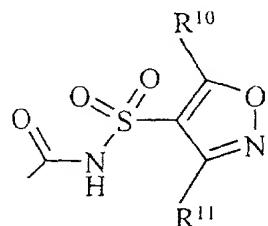
The applicants have found a particular substitution on the indole ring produces advantageous results when used therapeutically as inhibitors of MCP-1.

According to the present invention there is provided the use of a compound of formula (I)

5



(I)

10 X is CH<sub>2</sub> or SO<sub>2</sub>R<sup>1</sup> is an optionally substituted aryl or heteroaryl ring;R<sup>2</sup> is carboxy, cyano, -C(O)CH<sub>2</sub>OH, -CONHR<sup>8</sup>, -SO<sub>2</sub>NHR<sup>9</sup>, tetrazol-5-yl, SO<sub>3</sub>H, or a group of formula (VI)

15

(VI)

where R<sup>8</sup> is selected from hydrogen, alkyl, aryl, cyano, hydroxy, -SO<sub>2</sub>R<sup>12</sup> where R<sup>12</sup> is alkyl, aryl, heteroaryl, or haloalkyl, or R<sup>8</sup> is a group-(CHR<sup>13</sup>)<sub>r</sub>-COOH where r is an integer of 1-3 and each R<sup>13</sup> group is independently selected from hydrogen or alkyl; R<sup>9</sup> is hydrogen, alkyl, optionally substituted aryl such as optionally substituted phenyl or optionally substituted

20 heteroaryl such as 5 or 6 membered heteroaryl groups, or a group COR<sup>14</sup> where R<sup>14</sup> is alkyl, aryl, heteroaryl or haloalkyl; R<sup>10</sup> and R<sup>11</sup> are independently selected from hydrogen or alkyl, particularly C<sub>1-4</sub> alkyl;

R<sup>3</sup> is a group OR<sup>15</sup>, S(O)<sub>q</sub>R<sup>15</sup>, NHCOR<sup>16</sup>, NHSO<sub>2</sub>R<sup>16</sup>, (CH<sub>2</sub>)<sub>s</sub>COOH, (CH<sub>2</sub>)<sub>t</sub>CONR<sup>17</sup>R<sup>18</sup>, NR<sup>17</sup>R<sup>18</sup>, SO<sub>2</sub>NR<sup>17</sup>R<sup>18</sup> or optionally substituted alkenyl, where q is 0, 1 or 2, s is 0 or an integer of from 1 to 4, t is 0 or an integer of from 1 to 4, R<sup>15</sup> is a substituted alkyl or cycloalkyl group or an optionally substituted heteroaryl group, R<sup>16</sup> is optionally substituted alkyl,

5 optionally substituted aryl or optionally substituted heteroaryl and R<sup>17</sup> and R<sup>18</sup> are independently selected from hydrogen, optionally substituted alkyl, optionally substituted aryl and optionally substituted heteroaryl, with the proviso that at least one of R<sup>17</sup> or R<sup>18</sup> is other than hydrogen, or R<sup>16</sup> and R<sup>17</sup> together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring which optionally contains further

10 heteroatoms; and

R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are independently selected from hydrogen, a functional group or an optionally substituted hydrocarbyl groups or optionally substituted heterocyclic groups: for use in the preparation of a medicament for the inhibition of monocyte chemoattractant protein-1 and/or RANTES induced chemotaxis.

15 Pharmaceutically acceptable salts, esters and amides of compounds of formula (I) may also be used in this way.

In particular in the above formula s is an integer of from 1 to 4.

Suitably R<sup>4</sup> is other than a group OR<sup>18</sup>, S(O)<sub>m</sub>R<sup>18</sup>, NR<sup>19</sup>R<sup>20</sup>, C(O)NR<sup>19</sup>R<sup>20</sup>, NHCOR<sup>18</sup>, NHSO<sub>2</sub>R<sup>18</sup> or OCONR<sup>19</sup>R<sup>20</sup> or an alkyl group substituted by OR<sup>18</sup>, S(O)<sub>m</sub>R<sup>18</sup>, NR<sup>19</sup>R<sup>20</sup> where 20 R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup> and m are as defined hereinafter and R<sup>18</sup> is a substituted hydrogen-containing alkyl group.

Compounds of formula (I) are inhibitors of monocyte chemoattractant protein-1. In addition, they appear to inhibit RANTES induced chemotaxis. RANTES is another chemokine from the same family as MCP-1, with a similar biological profile, but acting 25 through the CCR1 receptor. As a result, these compounds can be used to treat disease mediated by these agents, in particular inflammatory disease. Thus the invention further provides a compound of formula (I) for use in preparation of a medicament for the treatment of inflammatory disease.

In this specification the term 'alkyl' when used either alone or as a suffix includes 30 straight chained, branched structures. These groups may contain up to 10, preferably up to 6 and more preferably up to 4 carbon atoms. Similarly the terms "alkenyl" and "alkynyl" refer to unsaturated straight or branched structures containing for example from 2 to 10, preferably

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from 2 to 6 carbon atoms. Cyclic moieties such as cycloalkyl, cycloalkenyl and cycloalkynyl are similar in nature but have at least 3 carbon atoms. Terms such as "alkoxy" comprise alkyl groups as is understood in the art.

The term "halo" includes fluoro, chloro, bromo and iodo. References to aryl groups 5 include aromatic carbocyclic groups such as phenyl and naphthyl. The term "heterocyclyl" includes aromatic or non-aromatic rings, for example containing from 4 to 20, suitably from 5 to 8 ring atoms, at least one of which is a heteroatom such as oxygen, sulphur or nitrogen. Examples of such groups include furyl, thienyl, pyrrolyl, pyrrolidinyl, imidazolyl, triazolyl, thiazolyl, tetrazolyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, 10 pyridazinyl, triazinyl, quinoliny, isoquinoliny, quinoxalinyl, benzothiazolyl, benzoxazolyl, benzothienyl or benzofuryl.

"Heteroaryl" refers to those groups described above which have an aromatic character. The term "aralkyl" refers to aryl substituted alkyl groups such as benzyl.

Other expressions used in the specification include "hydrocarbyl" which refers to any 15 structure comprising carbon and hydrogen atoms. For example, these may be alkyl, alkenyl, alkynyl, aryl, heterocyclyl, alkoxy, aralkyl, cycloalkyl, cycloalkenyl or cycloalkynyl.

The term "functional group" refers to reactive substituents. They may comprise 20 electron-donating or electron-withdrawing. Examples of such groups include halo, cyano, nitro,  $C(O)_nR^{18}$ ,  $OR^{18}$ ,  $S(O)_mR^{18}$ ,  $NR^{19}R^{20}$ ,  $C(O)NR^{19}R^{20}$ ,  $OC(O)NR^{19}R^{20}$ ,  $-NR^{19}C(O)_nR^{18}$ , -  $NR^{18}CONR^{19}R^{20}$ ,  $-N=CR^{18}R^{19}$ ,  $S(O)_nNR^{19}R^{20}$  or  $-NR^{19}S(O)_nR^{18}$  where  $R^{18}$ ,  $R^{19}$  and  $R^{20}$  are independently selected from hydrogen or optionally substituted hydrocarbyl, or  $R^{19}$  and  $R^{20}$  together with the atom to which they are attached, form an optionally substituted heterocyclyl ring as defined above which optionally contains further heteroatoms such as  $S(O)_n$ , oxygen and nitrogen,  $n$  is an integer of 1 or 2,  $m$  is 0 or an integer of 1-3.

25 Suitable optional substituents for hydrocarbyl groups  $R^{18}$ ,  $R^{19}$  and  $R^{20}$  include halo, perhaloalkyl such as trifluoromethyl, mercapto, hydroxy, carboxy, alkoxy, heteroaryl, heteroaryloxy, alkenyloxy, alkynyloxy, alkoxyalkoxy, aryloxy (where the aryl group may be substituted by halo, nitro, or hydroxy), cyano, nitro, amino, mono- or di-alkyl amino, oximino or  $S(O)_m$  where  $m$  is as defined above.

30 Where  $R^{19}$  and  $R^{20}$  together form a heterocyclic group, this may be optionally substituted by hydrocarbyl such as alkyl as well as those substituents listed above for hydrocarbyl groups  $R^{18}$ ,  $R^{19}$  and  $R^{20}$ .

Suitable substituents for hydrocarbyl or heterocyclic groups  $R^5$ ,  $R^6$  and  $R^7$  include those listed above for  $R^{18}$ ,  $R^{19}$  and  $R^{20}$ .

Suitably  $R^1$  is an optionally substituted phenyl, pyridyl, naphthyl, furyl or thienyl ring, and in particular is a substituted phenyl or pyridyl ring.

5      Suitable optional substituents for  $R^1$  in formula (I) include alkyl, alkenyl, alkynyl, halo, haloalkyl including perhaloalkyl such as trifluoromethyl, mercapto, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, hydroxyalkoxy, alkoxyalkoxy, alkanoyl, alkanoyloxy, cyano, nitro, amino, mono- or di-alkyl amino, oximino, sulphonamido, carbamoyl, mono or dialkylcarbamoyl or  $S(O)_m R^{21}$  where  $m$  is as defined above and  $R^{21}$  is hydrocarbyl.

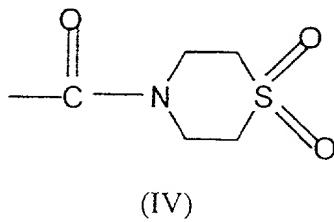
10     Suitably  $R^4$  is selected from hydrogen, hydroxy, halo, alkoxy, aryloxy or an optionally substituted hydrocarbyl group or optionally substituted heterocyclic group.

Particular examples of substituents  $R^4$  include hydrogen, hydroxy, halo, optionally substituted alkyl such as aralkyl, carboxyalkyl or the amide derivative thereof, alkoxy, or aryloxy.

15     Most preferably  $R^4$  is hydrogen.

Particular examples of substituents  $R^5$ ,  $R^6$  and  $R^7$  include hydrogen, hydroxy, halo, optionally substituted alkyl such as aralkyl, carboxyalkyl or the amide derivative thereof; alkoxy; aryloxy; aralkyloxy; or an amino group which is optionally substituted with alkyl, aryl or aralkyl. A specific functional group which is suitable for  $R^5$ ,  $R^6$  and/or  $R^7$  is a group of

20     sub-formula (IV).



25     Particular examples of groups  $R^5$ ,  $R^6$  and  $R^7$  are hydrogen, hydroxy, halo or alkoxy. In particular  $R^6$  and  $R^7$  are hydrogen.  $R^5$  may be hydrogen but in addition are suitably a small substituent such as hydroxy, halo or methoxy.

Particular substituents for  $R^1$  include trifluoromethyl,  $C_{1-4}$ alkyl, halo, trifluoromethoxy,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkanoyl,  $C_{1-4}$ alkanoyloxy, nitro, carbamoyl,  $30$   $C_{1-4}$ alkoxycarbonyl,  $C_{1-4}$ alkylsulphanyl,  $C_{1-4}$ alkylsulphinyl,  $C_{1-4}$ alkylsulphonyl, sulphonamido.

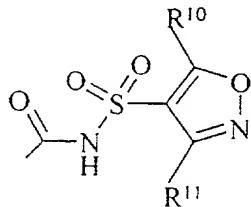
carbamoylC<sub>1-4</sub>alkyl, N-(C<sub>1-4</sub>alkyl)carbamoylC<sub>1-4</sub>alkyl, N-(C<sub>1-4</sub>alkyl)<sub>2</sub>carbamoyl-C<sub>1-4</sub>alkyl, hydroxyC<sub>1-4</sub>alkyl or C<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl.

Additionally or alternatively, two such substituents together may form a divalent radical of the formula -O(CH<sub>2</sub>)<sub>1-4</sub>O- attached to adjacent carbon atoms on the R<sup>1</sup> ring.

5 Preferred substituents for R<sup>1</sup> are one or more non-polar substituents such as halo.

In particular, R<sup>1</sup> is substituted by one or more halo groups, in particular chlorine. A particular example of an R<sup>1</sup> group is 3,4-dichlorophenyl, 3-fluoro-4-chlorophenyl, 3-chloro-4-fluorophenyl or 2,3-dichloropyrid-5-yl.

Examples of groups R<sup>2</sup> include carboxy; cyano; tetrazol-5-yl; SO<sub>3</sub>H; -CONHR<sup>8</sup> where 10 R<sup>8</sup> is selected from cyano, hydroxy, -SO<sub>2</sub>R<sup>12</sup> where R<sup>12</sup> is alkyl such as C<sub>1-4</sub>alkyl, aryl such as phenyl, heteroaryl or trifluoromethyl, or R<sup>8</sup> is a group-(CHR<sup>10</sup>)<sub>r</sub>-COOH where r is an integer of 1-3 and each R<sup>10</sup> group is independently selected from hydrogen or alkyl such as C<sub>1-4</sub>alkyl; or R<sup>2</sup> is a group -SO<sub>2</sub>NHR<sup>9</sup> where R<sup>9</sup> is an optionally substituted phenyl or an optionally substituted 5 or 6 membered heteroaryl group, or a group COR<sup>14</sup> where R<sup>14</sup> is alkyl such as 15 C<sub>1-4</sub>alkyl, aryl such as phenyl, heteroaryl or trifluoromethyl, or R<sup>2</sup> is a group of formula (VI)



(VI)

where R<sup>10</sup> and R<sup>11</sup> are independently selected from hydrogen or alkyl, particularly C<sub>1-4</sub>alkyl.

20 Preferably R<sup>2</sup> is carboxy or a pharmaceutically acceptable salt or ester thereof.

Particular groups R<sup>3</sup> include OR<sup>15</sup>, S(O)<sub>q</sub>R<sup>15</sup>, NHCOR<sup>16</sup>, NHSO<sub>2</sub>R<sup>16</sup>, SO<sub>2</sub>NR<sup>17</sup>R<sup>18</sup> where q, R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup> and R<sup>18</sup> are as defined above.

Suitable optional substituents for the group R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup> and R<sup>18</sup> as they appear in the definition of R<sup>3</sup>, or alkenyl groups R<sup>3</sup> as defined above include functional groups as

25 hereinbefore defined, as well as aryl or heteroaryl groups, either of which may themselves be substituted by one or more functional groups.

Particular examples of substituents for groups R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup> and R<sup>18</sup> include one or more groups selected from halo such as chloro, hydroxy, cyano, amino, mono- or di-

alkylamino,  $C_{1-4}$  alkoxy, carboxy, sulphonamido, CONH<sub>2</sub>, morpholino, pyridyl, pyrimidinyl, phenyl optionally substituted by halo such as chloro, carboxy, hydroxy, alkoxy such as methoxy, carbamoyl, acyl such as acetyl, or hydroxyalkyl where the alkyl group suitably includes at least two carbon atoms, such as hydroxyethyl.

5 Where R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup> and R<sup>18</sup> is a heteroaryl group, or where R<sup>17</sup> and R<sup>18</sup> together form an optionally substituted heterocyclic ring, these may be substituted by functional groups, or by alkyl groups such as methyl or ethyl, or alkenyl or alkynyl groups any of which may be substituted, for example with hydroxy.

10 A preferred group for R<sup>3</sup> is a group OR<sup>15</sup> straight or branched chain alkyl group which carries at least one hydroxy group, for example or 2 hydroxy groups. Other substituents, as defined above, may be provided on the alkyl chain.

15 Preferably R<sup>3</sup> is a group of formula -O(CH<sub>2</sub>)<sub>a</sub>[(CHOH)(CH<sub>2</sub>)<sub>b</sub>]<sub>d</sub>CH<sub>2</sub>OH where a is 0 or an integer of from 1 to 4, b is 0 or an integer of from 1 to 3, and d is 0, or 1.

Examples of such R<sup>3</sup> include OCH<sub>2</sub>CHOHCH<sub>2</sub>OH and OCH<sub>2</sub>CH<sub>2</sub>OH.

20 15 X is CH<sub>2</sub> or SO<sub>2</sub> and is preferably CH<sub>2</sub>.

25 Suitable pharmaceutically acceptable salts of compounds of formula (I) include acid addition salts such as methanesulfonate, fumarate, hydrochloride, hydrobromide, citrate, maleate and salts formed with phosphoric and sulphuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, N-methylpiperidine, N-ethylpiperidine, procaine, dibenzylamine, N,N-dibenzylethylamine or amino acids for example lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically acceptable salt is a sodium salt.

30 25 An *in vivo* hydrolysable ester of a compound of the formula (I) containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol.

35 Suitable pharmaceutically acceptable esters for carboxy include alkyl esters, such as  $C_{1-6}$  alkyl esters for example, ethyl esters,  $C_{1-6}$  alkoxyethyl esters for example methoxymethyl,  $C_{1-6}$  alkanoyloxyethyl esters for example pivaloyloxyethyl, phthalidyl esters,  $C_{3-8}$  cycloalkoxy-carbonyloxy $C_{1-6}$  alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example

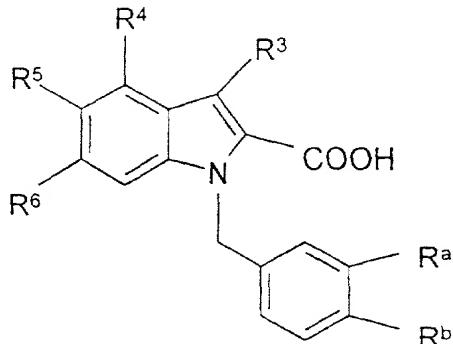
5-methyl-1,3-dioxolen-2-onylmethyl; and C<sub>1-6</sub>alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

Suitable pharmaceutically acceptable esters of compounds of formula (I) are *in vivo* hydrolysable ester of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and  $\alpha$ -acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of  $\alpha$ -acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxy carbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

Esters which are not *in vivo* hydrolysable are useful as intermediates in the production of the compounds of formula (I) and therefore these form a further aspect of the invention.

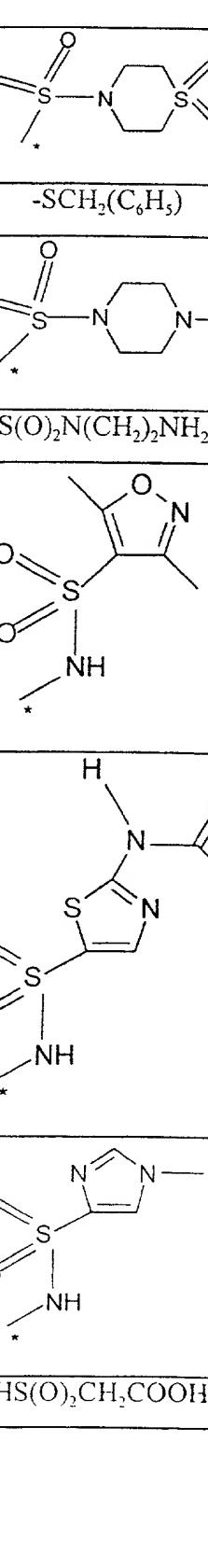
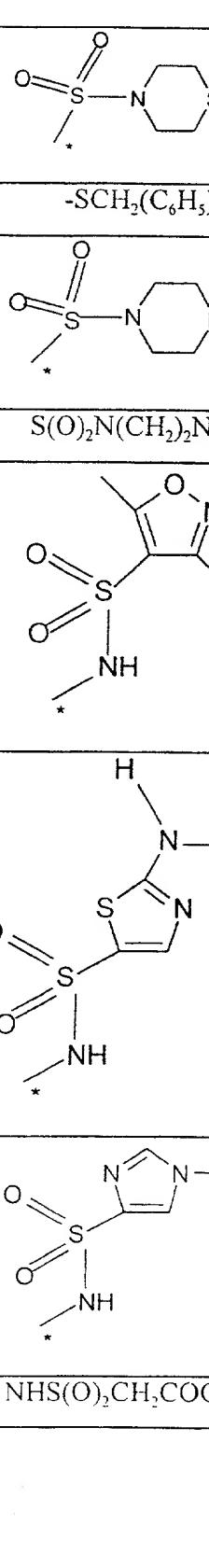
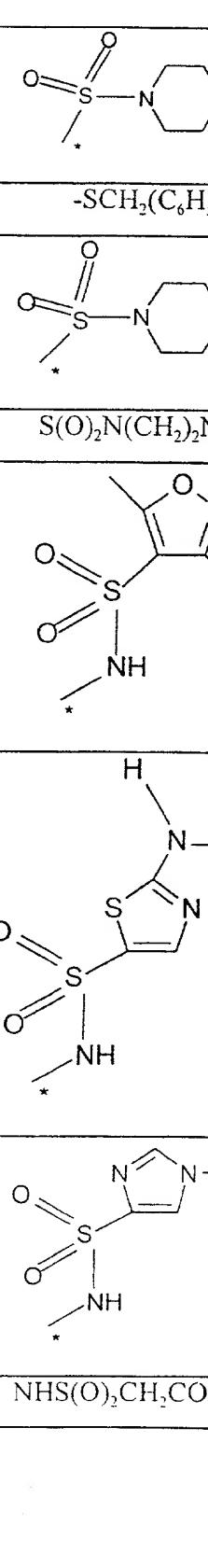
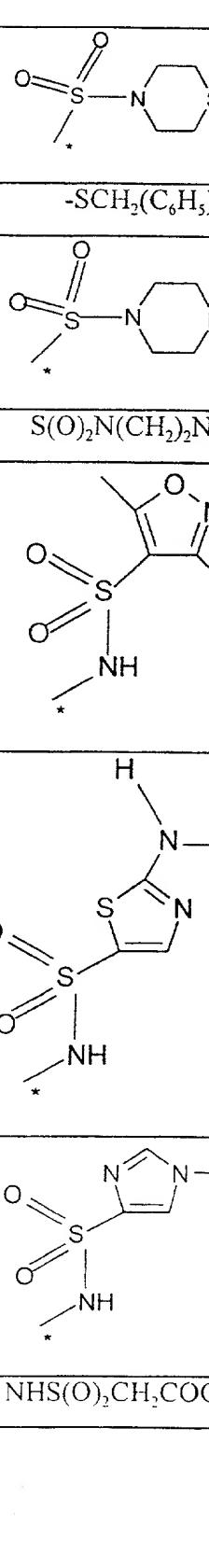
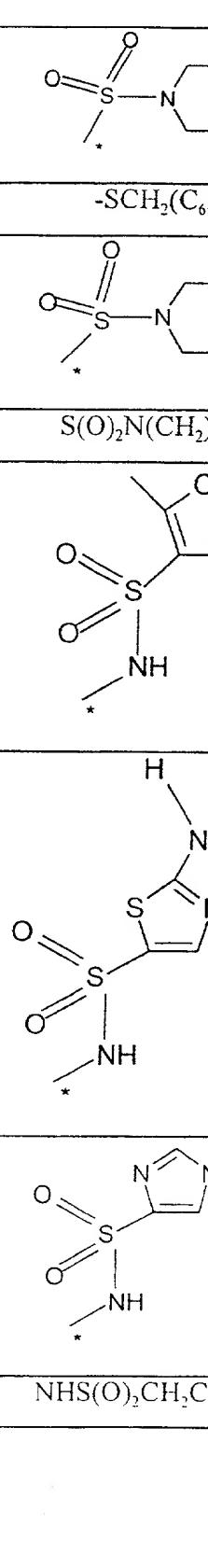
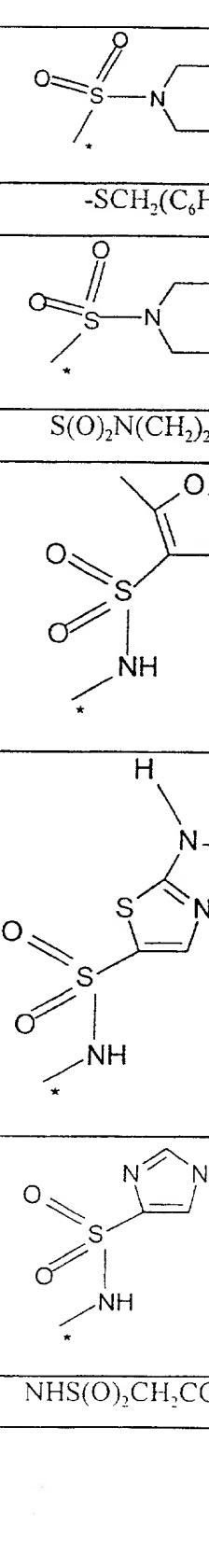
Thus examples of compounds of formula (I) include the following:

Table 1

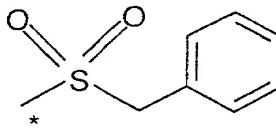
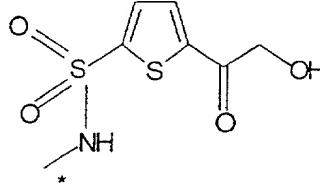
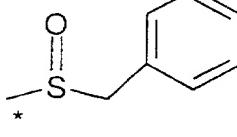
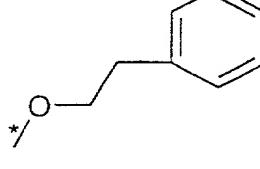
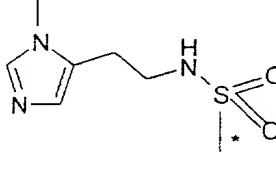
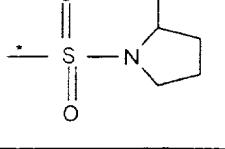
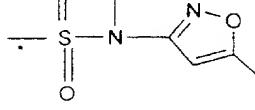


20

Compd No.	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	R <sup>6</sup>	R <sup>a</sup>	R <sup>b</sup>
1		H	H	H	Cl	Cl

2	-NHS(O) <sub>2</sub> CH <sub>3</sub>	H	H	H	Cl	Cl
3		H	H	H	Cl	Cl
4		H	H	H	Cl	Cl
5	-SCH <sub>2</sub> (C <sub>6</sub> H <sub>5</sub> )	H	H	H	Cl	Cl
6		H	H	H	Cl	Cl
7	S(O) <sub>2</sub> N(CH <sub>2</sub> ) <sub>2</sub> NH <sub>2</sub>	H	H	H	Cl	Cl
8		H	H	H	Cl	Cl
9		H	H	H	Cl	Cl
10		H	H	H	Cl	Cl
11	NHS(O) <sub>2</sub> CH <sub>2</sub> COOH	H	H	H	Cl	Cl

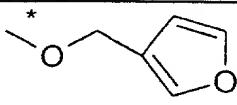
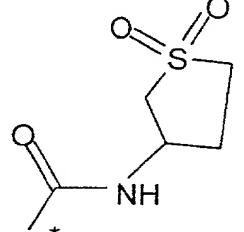
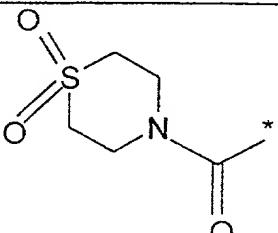
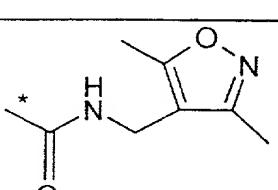
12		H	H	H	Cl	Cl
13		H	H	H	Cl	Cl
14	NHC(O)CH <sub>2</sub> COOH	H	H	H	Cl	Cl
15	NHC(O)CH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub>	H	H	H	Cl	Cl
16		H	H	H	Cl	Cl
17	NHC(O)CH(OH)CH <sub>3</sub>	H	H	H	Cl	Cl
18		H	H	H	Cl	Cl
19		H	H	H	Cl	Cl
20		H	H	H	Cl	Cl

21		H	H	H	Cl	Cl
22		H	H	H	Cl	Cl
23	OCH <sub>2</sub> CH <sub>2</sub> OH	H	H	H	Cl	Cl
24	SCH <sub>2</sub> C(O) <sub>2</sub> H	H	H	H	Cl	Cl
25		H	H	H	Cl	Cl
26		H	H	H	Cl	Cl
27	OCH <sub>2</sub> COOH	H	H	H	Cl	Cl
28	CH <sub>2</sub> COOH	H	H	H	Cl	Cl
29	S(O <sub>2</sub> )NH(CH <sub>2</sub> ) <sub>2</sub> OH	H	H	H	Cl	Cl
30	S(O <sub>2</sub> )N((CH <sub>2</sub> ) <sub>2</sub> OH) <sub>2</sub>	H	H	H	Cl	Cl
31		H	H	H	Cl	Cl
32		H	H	H	Cl	Cl
33		H	H	H	Cl	Cl

34		H	H	H	Cl	-Cl
35		H	H	H	Cl	Cl
36		H	H	H	Cl	Cl
37		H	H	H	Cl	Cl
38	$S(O)_2NHCH_2CH(OCH_3)_2$	H	H	H	Cl	Cl
39	$S(O)_2NHCH_2C\equiv CH$	H	H	H	Cl	Cl
40	$S(O)_2N((CH_2)_2OCH_3)_2$	H	H	H	Cl	Cl
41		H	H	H	Cl	Cl
42		H	H	H	Cl	Cl
43		H	H	H	Cl	Cl
44		H	H	H	Cl	Cl
45		H	H	H	Cl	Cl
46		H	H	H	Cl	Cl
47	$S(O)_2NH(CH_2)_2NS(O)_2N(CH_3)_2$	H	H	H	Cl	Cl
48		H	H	H	Cl	Cl

49	CH <sub>2</sub> C(O)NHCH <sub>2</sub> CH <sub>2</sub> OH	H	H	H	Cl	Cl
50	CH=CHCOOH	H	H	H	Cl	Cl
51	S(O) <sub>2</sub> CH <sub>2</sub> COOH	H	H	H	Cl	Cl
52	CH <sub>2</sub> C(O)N(CH <sub>3</sub> )-(CH <sub>2</sub> ) <sub>2</sub> OH	H	H	H	Cl	Cl
53		H	H	H	Cl	Cl
54		H	H	H	Cl	Cl
55	CH <sub>2</sub> C(O)N(CH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub> ) <sub>2</sub>	H	H	H	Cl	Cl
56	CH <sub>2</sub> C(O)NHCH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub>	H	H	H	Cl	Cl
57		H	H	H	Cl	Cl
58		H	H	H	Cl	Cl
59		H	H	H	Cl	Cl
60		H	H	H	Cl	Cl
61		H	H	H	Cl	Cl
62	CH <sub>2</sub> C(O)NHCH <sub>2</sub> C(O)(CH <sub>2</sub> ) <sub>2</sub> COO	H	H	H	Cl	Cl

63		H	H	H	Cl	Cl
64		H	H	H	Cl	Cl
65		H	H	H	Cl	Cl
66	O(CH <sub>2</sub> ) <sub>2</sub> OCH <sub>3</sub>	H	H	H	Cl	Cl
67	OCH <sub>2</sub> CH <sub>2</sub> NHC(O)OC(CH <sub>3</sub> ) <sub>3</sub>	H	H	H	Cl	Cl
68		H	H	H	Cl	Cl
69	OCH <sub>2</sub> CH <sub>2</sub> NH <sub>2</sub>	H	H	H	Cl	Cl
70		H	H	H	Cl	Cl
71	OCH <sub>2</sub> CHOHCH <sub>2</sub> OH	H	H	H	Cl	Cl
72		H	H	H	Cl	Cl
73		H	H	H	Cl	Cl
74		H	H	H	Cl	Cl
75		H	H	H	Cl	Cl
76		H	H	H	Cl	Cl

77		H	H	H	Cl	Cl
78		H	H	H	Cl	Cl
79		H	H	H	Cl	Cl
80		H	H	H	Cl	Cl
81		H	H	H	Cl	Cl
82	OCH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> CH <sub>3</sub>	H	OCH <sub>3</sub>	H	Cl	Cl
83	OCH <sub>2</sub> CH <sub>2</sub> OH	H	OCH <sub>3</sub>	H	Cl	Cl
84		H	H	H	Cl	Cl
85		H	H	H	Cl	Cl
86	COOH	H	H	H	Cl	Cl

where \* indicates the point of attachment of the group to the indole ring.

Some compounds of formula (I) have not been proposed hitherto for use as pharmaceuticals. Thus a further aspect of the invention provides a compound for use in therapy, said compound comprising a compound of formula (1A) which is a compound of formula (I) as defined above subject to the following provisos:

(i) when R<sup>2</sup> is carboxy or a salt or amide thereof, at least three of R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are hydrogen, and R<sup>3</sup> is S(O)qR<sup>15</sup>, R<sup>15</sup> is other than C<sub>1-4</sub> alkyl substituted by carboxy or an ester or amide derivative thereof;

(ii) when R<sup>3</sup> is a group NHCOR<sup>16</sup> or NHSO<sub>2</sub>R<sup>16</sup>, R<sup>16</sup> is optionally substituted alkyl; and

5 (iii) where R<sup>3</sup> is a group SR<sup>14</sup> where R<sup>14</sup> is 2-quinolylmethyl, R<sup>2</sup> is COOH or an ethyl ester thereof, each of R<sup>4</sup>, R<sup>5</sup>, and R<sup>7</sup> are hydrogen, R<sup>1</sup> is 4-chlorophenyl, R<sup>6</sup> is other than 2-quinolylmethyl.

Yet a further aspect of the invention provides pharmaceutical compositions comprising a compound of formula (IA) as defined above.

10 Certain compounds of formula (I) are novel and these form a further aspect of the invention. Thus the invention further provides a compound of formula (IB) which is a compound of formula (IA) as defined above, subject to the following further provisos:

(iv) where R<sup>3</sup> is a group CH<sub>2</sub>COOH, R<sup>2</sup> is COOH and each of R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are hydrogen, R<sup>1</sup> is other than unsubstituted phenyl; and

15 (v) where R<sup>3</sup> is a group CH<sub>2</sub>COOH, R<sup>2</sup> is COOH and each of R<sup>4</sup>, R<sup>5</sup>, and R<sup>7</sup> are hydrogen, R<sup>1</sup> is 4-chlorophenyl, R<sup>6</sup> is other than methoxy; and

(vi) when R<sup>3</sup> is OR<sup>15</sup> or S(O)<sub>q</sub>R<sup>15</sup>, R<sup>15</sup> is other than C<sub>1-6</sub> haloalkyl.

Yet a further proviso which is suitably applied to formula (IB) is

(vii) when R<sup>2</sup> is COOCH<sub>2</sub>CH<sub>3</sub>, each of R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are hydrogen and R<sup>1</sup> is 4-chlorophenyl, R<sup>3</sup> is other than a group CH=CH(CN)<sub>2</sub>.

Furthermore, the proviso (iv') suitably applies to (IA) in that where R<sup>3</sup> is a group COOH, R<sup>2</sup> is COOH and each of R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are hydrogen, R<sup>1</sup> is other than unsubstituted phenyl.

Particularly preferred substituents and groups on the compounds of formula (IA) and  
25 (IB) are those described above in relation to formula (I).

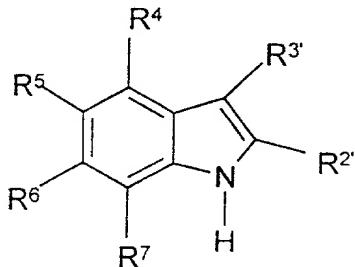
Suitable examples of compounds of formula (IB) are compounds where R<sup>3</sup> is a group OR<sup>15</sup> straight or branched chain alkyl group which carries at least one hydroxy group, for example from 1 to 4 hydroxy groups, for example 1 or 2 hydroxy groups. Other substituents, as defined above, may be provided on the alkyl chain.

30 Preferably R<sup>3</sup> is a group of formula -O(CH<sub>2</sub>)<sub>a</sub>[(CHOH)(CH<sub>2</sub>)<sub>b</sub>]<sub>d</sub>CH<sub>2</sub>OH where a is 0 or an integer of from 1 to 4, b is 0 or an integer of from 1 to 3, and d is 0 or 1.

Examples of such R<sup>3</sup> include OCH<sub>2</sub>CHOHCH<sub>2</sub>OH and OCH<sub>2</sub>CH<sub>2</sub>OH.

Compounds of formula (I) are suitably prepared by methods such as those described in International Patent Application Nos. PCT/GB98/02340 and PCT/GB98/02341.

In particular compounds of formula (I) can be prepared by reacting a compound of formula (VII)

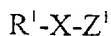


5

(VII)

where R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are as defined in relation to formula (I), R<sup>2'</sup> is a group R<sup>2</sup> as defined in relation to formula (I) or a protected form thereof, and R<sup>3'</sup> is a group R<sup>3</sup> as defined in relation to formula (I) or a precursor thereof; with compound of formula (VIII)

10



(VIII)

where R<sup>1</sup> and X are as defined in relation to formula (I) and Z<sup>1</sup> is a leaving group; and  
15 thereafter if desired or necessary carrying out one or more of the following steps:

- (i) changing a precursor group R<sup>3'</sup> to a group R<sup>3</sup> or a group R<sup>3</sup> to a different such group;
- (ii) removing any protecting group from R<sup>2'</sup>.

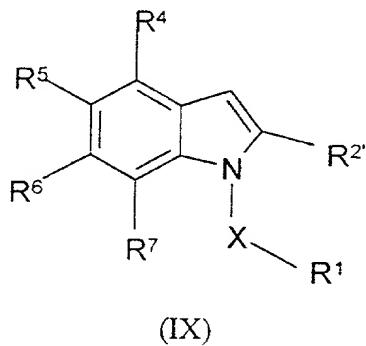
Suitable leaving groups for Z include halide such as chloride, bromide or iodide, as  
20 well as mesylate or tosylate. The reaction is suitably effected in an organic solvent such as dimethylformamide (DMF) tetrahydrofuran (THF) or DCM in the presence of a base such as sodium hydride, sodium hydroxide, potassium carbonate. Optionally the reaction is effected in the presence of a suitable phase transfer catalyst. The choice of base and solvent is interdependent to a certain extent in that certain solvents are compatible with some bases only  
25 as is understood in the art. For example, sodium hydride may preferably be used with dimethylformamide or tetrahydrofuran and sodium hydroxide is preferably used with dichloromethane and a phase transfer catalyst.

The reaction can be carried out at moderate temperatures, for example from 0 to 50°C and conveniently at about ambient temperature.

Preferably, R<sup>2</sup> is an ester group in the compound of formula (VII) and this may be subsequently converted to an acid or to another ester or salt, by conventional methods. For 5 example, when X is a group SO<sub>2</sub> and R<sup>2</sup> is a methyl ester of carboxy, it may be converted to the corresponding carboxylic acid by reaction with lithium iodide in dry pyridine or DMF.

Optional step (i) and (ii) above can be carried out using conventional methods. These will depend upon the precise nature of the groups R<sup>1</sup>, R<sup>3</sup>, R<sup>2</sup> and R<sup>2'</sup> in each case. Examples of suitable reactions are illustrated hereinafter.

10 Alternatively, compounds of formula (I) may be prepared by reacting a compound of formula (IX)



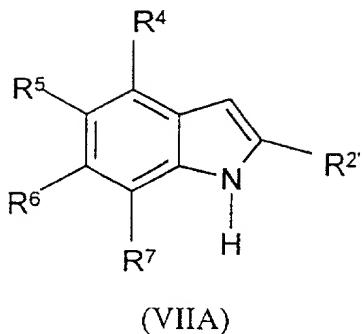
where X, R<sup>1</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are as defined in relation to formula (I), R<sup>2'</sup> is a group R<sup>2</sup> as 15 defined in relation to formula (I) or a protected form thereof; with a compound of formula (X)



where R<sup>3</sup> is a group R<sup>3</sup> as defined in relation to formula (I) or a precursor thereof; and 20 thereafter if desired or necessary carrying out steps (i) and/ or (ii) above.

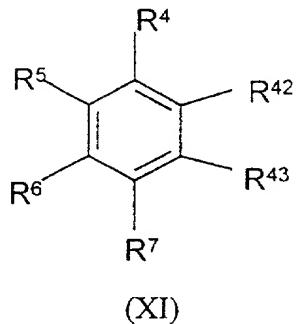
The reaction is suitably carried out in an organic solvent which will depend upon the nature of the compound of formula (IX). Suitable leaving groups Z<sup>1</sup> include those listed above for Z.

Compounds of formula (IX) may suitably be prepared by methods analogous to those 25 described above between the compound of formula (VII) and (VIII), although in this case, a compound of formula (VIIA) will be used.



In this compound, R<sup>2'</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are as defined above.

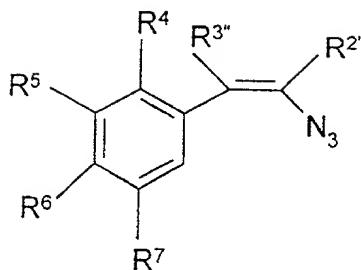
Compounds of formula (VII) and (VIIA) may be prepared by cyclisation of a 5 compound of formula (XI)



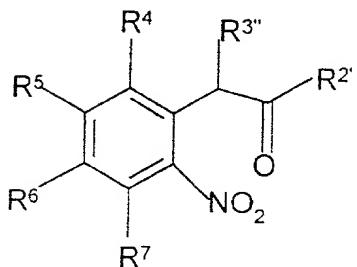
where R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are as defined above and R<sup>42</sup> and R<sup>43</sup> represent a combination of 10 moieties which can cyclise to form an appropriately substituted pyrrole ring. For example, R<sup>42</sup> can be a group of formula -CH=C(R<sup>44</sup>)N<sub>3</sub> where R<sup>44</sup> is a group R<sup>2</sup> as defined above, or a protected form thereof, and R<sup>43</sup> may be hydrogen. Cyclisation to form a compound of formula (XII) may then be effected by heating for example under reflux in an organic solvent, in particular a high boiling aprotic solvent such as xylene or toluene.

15 Alternatively, R<sup>43</sup> may be nitro and R<sup>42</sup> may be a group of formula -CH<sub>2</sub>C(O)R<sup>2'</sup> where R<sup>2'</sup> is as defined above in relation to formula (VII). These compounds will cyclise in the presence of a catalyst such as palladium on carbon in the presence of hydrogen. The reaction may be effected at moderate temperatures for example of from 0 to 80°C, conveniently at about ambient temperature.

20 Thus examples of compounds of formula (XI) include compounds of formula (XII) and (XIII)



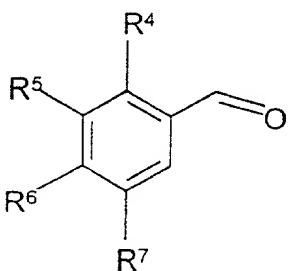
(XIII)



(XIV)

where  $R^{2'}$ ,  $R^4$ ,  $R^5$ ,  $R^6$  and  $R^7$  are as hereinbefore defined and  $R^{3''}$  is a group  $R^3$  or is hydrogen, which may be converted later to a group  $R^3$  or  $R^3'$ .

Compounds of formula (XIII) where  $R^3$  is hydrogen may be prepared for example by  
10 reacting a compound of formula (XV)



(XV)

with a compound of formula (XVI)

15



(XVI)

where  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$ , and  $R^{2'}$  are as defined hereinbefore. The reaction may be effected in an organic solvent such as ethanol at low temperatures of from -20 to 0°C, suitably at about 0°C.

The reaction is suitably effected in the presence of a base such as an alkoxide, in particular an ethoxide, for example potassium ethoxide.

Compounds of formula (XVI) are suitably prepared by reacting a compound of formula (XVII)

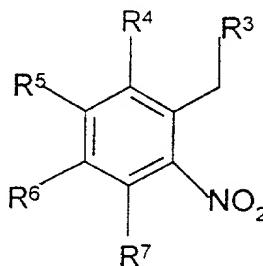
5



(XVII)

where  $R^3$  and  $R^{2'}$  are as defined above and  $R^{47}$  is a leaving group such as halide and in particular bromide, with an azide salt, such as an alkali metal azide salt in particular sodium azide.

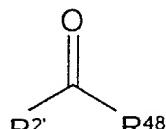
10 Compounds of formula (XIV) may be prepared by reacting a compound of formula (XVIII)



(XVIII)

where  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^3$ ,  $R^4$  and  $R^{2'}$  are as defined above, with a compound of formula (XIX)

15



(XIX)

where  $R^{2'}$  is as defined above and  $R^{48}$  leaving group such as hydroxy. Examples of 20 compounds of formula (XVI) are oxalates such as diethyloxalate. The reaction is suitably effected in the presence of a base such as sodium hydride in an organic solvent such as THF. Moderate temperatures of from 0° to 40°C and conveniently ambient temperature is employed.

25 According to a further aspect of the invention there is provided a compound of the formula (I) as defined herein, or a pharmaceutically acceptable salt or an *in vivo* hydrolysable

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ester thereof, for use in a method of treatment of the human or animal body by therapy. In particular, the compounds are used in methods of treatment of inflammatory disease.

According to a further aspect of the present invention there is provided a method for antagonising an MCP-1 mediated effect in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, or an *in vivo* hydrolysable ester thereof.

The invention also provides a compound of formula (I) as defined herein, or a pharmaceutically acceptable salt, or an *in vivo* hydrolysable ester thereof, for use as a medicament.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl *p*-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal track, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

5 Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxyethylene stearate), or

10 condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters

15 derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening

20 agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents 25 may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

10 Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using 15 one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedure well known in the art.

Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30 $\mu$  or much less, the powder itself comprising either active ingredient alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then conveniently retained in a capsule containing, for example, 1 to 50mg of active ingredient for

use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing 5 finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on Formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial 10 Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent 15 compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial 20 Board), Pergamon Press 1990.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine. As mentioned above, compounds of the Formula I are useful in 25 treating diseases or medical conditions which are due alone or in part to the effects of farnesylation of rats.

In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be 30 administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for

example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred.

The invention is further illustrated, but not limited by the following Examples in which the following general procedures were used unless stated otherwise.

5

### Preparation 1

#### Ethyl 3-bromoindole-2-carboxylate

A solution of bromine (2.72 ml) in DMF was added dropwise over 10 mins to a solution of ethyl indole-2-carboxylate in DMF. The reaction was stirred for 30 mins, then 10 poured into water to precipitate a pale yellow solid which was filtered off and recrystallized from ethyl acetate to give the desired starting material as white needles (10.2 g, 72%), mp 150-151°; NMR d (CDCl<sub>3</sub>) 1.44 (t, 3H), 4.45 (q, 2H), 7.22 (m, 1H), 7.38 (m, 2H), 7.66 (d, 1H), 9.27 (brs, 1H); M/z (-) 268 (M<sup>+</sup>), 266, 196, 194.

15

#### Ethyl 3-benzylthioindole-2-carboxylate

Potassium carbonate (3.5 g) was added to a solution of ethyl 3-bromoindole-2-carboxylate (5.4 g) and benzyl mercaptan (3.05 ml) in DMF (100 ml), and the reaction heated at 100°C for 3 hours. The reaction was then cooled, poured into water and 20 extracted with ethyl acetate. Combined organic extracts were washed with water and brine, dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The residue was purified by column chromatography using *iso*-hexane : 5% ethyl acetate as eluent, to give the product as a white crystalline solid (3.48 g, 56%); NMR d (CDCl<sub>3</sub>) 1.42 (t, 3H), 4.05 (s, 2H), 4.40 (q, 2H), 7.10 - 7.40 (m, 8H), 7.78 (d, 1H), 9.06 (brs, 1H); M/z (+) 312 (M<sup>+</sup>), 266, 166.

25

### Preparation 3

#### Ethyl 3-(ethoxycarbonylmethylthio)indole-2-carboxylate

To a solution of ethyl 3-bromoindole-2-carboxylate (1.34 g) and ethyl 2-mercaptoproacetate (0.96 ml) in acetone (15 ml) was added potassium carbonate (1.38 g) and the 30 resulting mixture was heated at reflux under argon for 18 hours. The cooled mixture was poured into water and extracted with ethyl acetate. Combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated to a gum which was purified by column chromatography using *iso*-

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hexane : ethyl acetate (1:4) to give the desired product (331 mg, 21%) NMR d ( $\text{CDCl}_3$ ) 1.05 (t, 3H), 1.45 (t, 3H), 3.6 (s, 2H), 4.0 (q, 2H), 4.5 (q, 2H), 7.2 - 7.4 (m, 3H), 7.9 (d, 1H), 9.2 (brs, 1H);  $M/z$  (+) 308.3 ( $M^+$ ).

## 5 Preparation 4

### Ethyl N-(3,4-dichlorobenzyl)-3-(morpholinosulphinyl)indole-2-carboxylate

Thionyl chloride (5 ml) was added in one portion to a solution of ethyl *N*-(3,4-dichlorobenzyl)indole-2-carboxylate (908 mg) and the resulting mixture was stirred for 18 hours. The mixture was concentrated *in vacuo*. The resulting gum was suspended in diethyl ether (12 ml) and morpholine (2.2 ml) was added in one portion. The mixture was stirred for 3 hours. The reaction was quenched with water (10 ml) extracted with dichloromethane, dried ( $\text{MgSO}_4$ ) and concentrated to a gum which was purified by column chromatography using *iso*-hexane : ethyl acetate (1:1) as eluent to give the desired product (907 mg, 72%); NMR d ( $\text{CDCl}_3$ ) 1.4 (t, 3H), 3.0 - 3.1 (m, 2H), 3.3 - 3.4 (m, 2H), 3.7 - 3.8 (m, 4H), 4.4 (q, 2H), 5.7 (q, 2H), 6.8 (d, 1H), 7.1 (d, 1H), 7.25 - 7.4 (m, 4H), 8.6 (d, 1H);  $M/z$  (-) 480 ( $M^+$ ).

## Preparation 5

The procedure described in Preparation 4 above was repeated using the appropriate amine. Thus was obtained the compound described below.

20

### Ethyl N-(3,4-dichlorobenzyl)-3-(1,1-dioxidothiomorpholino)sulphinylinole-2-carboxylate

52% yield; NMR d ( $\text{CDCl}_3$ ) 1.4 (t, 3H), 3.1 - 3.3 (m, 4H), 3.7-4.0 (4H, m), 4.4 (q, 2H), 5.7 (q, 2H), 6.8 (d, 1H), 7.1 (s, 1H), 7.3 - 7.5 (m, 4H), 8.6 (d, 1H);  $M/z$  (-) 529.1 ( $M^+$ ), 527.1.

25

## Preparation 6

### N-(3,4-Dichlorobenzyl)-2-ethoxycarbonylindole-3-sulphinic acid

Ethyl *N*-(3,4-dichlorobenzyl)indole-2-carboxylate (1.11 g) in thionyl chloride (4.0 ml) was stirred for 16 hours, then concentrated *in vacuo*. The residue was dissolved in THF (10 ml) and water (2 ml), and stirred for a further 2 hours. The reaction was partitioned between ether and water. Combined organic extracts were dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo* and the residue triturated with ether to give the product as a white solid (0.67 g, 51%); NMR d

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(CD<sub>3</sub>SOCD<sub>3</sub>) 1.27 (t, 3H), 4.35 (q, 2H), 5.80 (s, 2H), 6.83 (d, 1H), 7.23 (t, 1H), 7.40 (m, 2H), 7.57 (d, 1H), 7.68 (d, 1H), 8.42 (d, 1H); *M/z* (-) 412 (*M*<sup>+</sup>), 410, 348, 346.

### Preparation 7

#### 5 N-(3,4-Dichlorobenzyl)-2-ethoxycarbonylindole-3-sulphonyl chloride

N-(3,4-Dichlorobenzyl)-2-ethoxycarbonylindole-3-sulphinic acid (0.48 g), *N*-chlorosuccinimide (0.16 g) and triethylamine (0.16 ml) were stirred in dichloromethane for 4 hours. The reaction was then concentrated *in vacuo* and the residue purified by chromatography using *iso*-hexane : 10% ethyl acetate as eluent to give the product as a white 10 crystalline solid (0.27 g, 52%); NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 1.43 (t, 3H), 4.48 (q, 2H), 5.53 (s, 2H), 6.98 (m, 1H), 7.30 - 7.50 (m, 5H), 8.22 (m, 1H); *M/z* (-) 444 (*M*-H<sup>+</sup>), 426, 410.

### Preparation 8

#### Ethyl 3-diazoindole-2-carboxylate

15 Acetic acid (77 ml) was added dropwise to a suspension of sodium nitrite (82 g) and ethyl indole-2-carboxylate (25 g) in dichloromethane (1000 ml), and stirred at ambient temperature under inert atmosphere. After 2 days, further sodium nitrite (20 g) was added, and acetic acid (19 ml) was added dropwise, and the reaction left stirring for a further day. The reaction was poured into water (300 ml), extracted with dichloromethane (2 x 200 ml), and 20 neutralised with saturated sodium hydrogen carbonate solution (300 ml). Combined organic extracts were dried (MgSO<sub>4</sub>), and concentrated *in vacuo* to afford the product as a yellow solid (26.96 g, 95%), NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 1.34 (t, 3H), 4.37 (q, 2H), 7.38 (m, 2H), 7.84 (m, 2H); *M/z* (+) 216.2 (*MH*<sup>+</sup>).

### 25 Preparation 9

#### Ethyl 3-diazo-5-methoxyindole-2-carboxylate (precursor to compound 83, 84)

To a solution of ethyl 5-methoxyindole-2-carboxylate (8.0 g) in acetone (300 ml) was added a solution of sodium nitrite (39 g) in water (100 ml) and the reaction stirred vigorously while adding dropwise HCl (2M, 98 ml) at 20-25°C during one hour. The mixture was stirred 30 in a stoppered flask at 20°C overnight and the resulting yellow precipitate was filtered to give the product (6.0 g, 67%); NMR d (CDCl<sub>3</sub>) 1.45 (t, 3H), 3.87 (s, 3H), 4.50 (q, 2H), 6.98 (m, 2H), 7.85 (d, 1H); *M/z* (+) 246 (*MH*<sup>+</sup>).

**Preparation 10****t-Butyl 3-bromo-N-(3,4-dichlorobenzyl)indole-2-carboxylate**

*N,N*-dimethylformamide di-*t*-butyl acetal (19.90 ml) was added dropwise to a 5 suspension of 3-bromo-*N*-(3,4-dichlorobenzyl)indole-2-carboxylic acid (8.31 g) in toluene (150 ml), under an atmosphere of argon, and stirred at ambient temperature for 2 hours. The reaction was cooled, filtered, and washed with brine (100 ml), saturated  $\text{NaHCO}_3$  (aq.) (100 ml), and brine (100 ml), dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo* to afford the product as a clear oil that crystallised upon standing (7.65 g, 81%); NMR d ( $\text{CD}_3\text{SOCD}_3$ ) 1.49 (s, 9H), 5.76 10 (s, 2H), 6.86 (m, 1H), 7.24 (t, 1H), 7.35-7.68 (m, 5H); *M/z* (+) 456 ( $\text{MH}^+$ ). 400.

**Preparation 11****Methyl 2-methoxycarbonyl-3-indoleacetate**

Phenyl hydrazine (5.7 ml), dimethyl 2-oxoglutarate (10 g) and acetic acid (1.0 ml) in 15 methanol (100 ml) were heated at reflux for 1 hour, then concentrated *in vacuo*. The crude hydrazone (13 g) was dissolved in saturated methanolic hydrochloric acid (350 ml) and heated to 75°C for 16 hours with continual stirring. The reaction was diluted with water (200 ml) and extracted with dichloromethane. Combined organic extracts were washed with saturated aqueous sodium hydrogencarbonate solution, water, saturated aqueous sodium chloride 20 solution and dried ( $\text{MgSO}_4$ ). The solvent was removed *in vacuo* to give a yellow crystalline solid (7.0 g); NMR d ( $\text{CD}_3\text{SOCD}_3$ ) 3.59 (s, 3H), 3.83 (s, 3H), 4.12 (s, 2H), 7.06 (t, 1H), 7.26 (t, 1H), 7.41 (d, 1H), 7.63 (d, 1H), 11.76 (brs, 1H); *M/z* (-) 246 ( $\text{M}-\text{H}^+$ ).

**Preparation 12****Methyl N-(3,4-dichlorobenzyl)-2-methoxycarbonyl-3-indoleacetate**

3,4-Dichlorobenzyl chloride (8.2 g) was added to a stirred solution of methyl 2-methoxycarbonyl-3-indoleacetate (6.5 g) and potassium carbonate (8.36 g) in acetonitrile (200 ml) under an atmosphere of argon. The reaction was heated to 80°C for 24 hours. The reaction was concentrated *in vacuo* and partitioned between ethyl acetate and water. 30 Combined organic extracts were washed with saturated aqueous sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo*. The residue was purified by column chromatography using 25% ethyl acetate : *iso*-hexane as eluent to give the product as a white

solid (6.95 g, 65%); NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 3.60 (s, 3H), 3.77 (s, 3H), 4.13 (s, 2H), 5.89 (s, 2H), 6.89 (dd, 1H), 7.16 (t, 1H), 7.27 (d, 1H), 7.34 (t, 1H), 7.52 (d, 1H), 7.57 (d, 1H), 7.78 (d, 1H); *M/z* (+) 406 (MH<sup>+</sup>).

## 5 Preparation 13

### Methyl 3-aminoindole-2-carboxylate

To a solution of ethyl 3-aminoindole-2-carboxylate [Prepared according to P. Unangst, *J. Het. Chem.*, 1983, **20**, 495] (5.0 g) in methanol (50 ml) was added sodium methoxide (6.5 g). The resulting mixture was stirred for 4 hours and then quenched with saturated ammonium chloride solution. The

10 resulting mixture was extracted with dichloromethane, dried (MgSO<sub>4</sub>) and evaporated to give a gum which was purified by column chromatography using *iso*-hexane : ethyl acetate (1:4) as eluent to give the desired product (1.95 g, 42%); NMR d (CD<sub>3</sub>SOCD<sub>3</sub>), 3.8 (s, 3H), 5.7 (s, 2H), 6.8 - 6.9 (m, 1H), 7.2 (m, 2H), 7.7 (d, 1H); *M/z* (+) 191.1 (MH<sup>+</sup>).

## 15 Preparation 14

### Ethyl 3-formylindole-2-carboxylate

A mixture of *N*-methylformanilide (2.25 ml) and phosphoryl chloride (1.70 ml) was stirred at ambient temperature for 15 minutes. 1,2-dichloroethane (30 ml) was then added, followed by ethyl indole-2-carboxylate (3 g) and the reaction was heated at reflux for 90

20 minutes. The reaction mixture was then poured into a mixture of ice / water (200 ml) and sodium acetate (10 g) and extracted with ethyl acetate (2 x 200 ml). Combined organic phases were evaporated and the crude residue purified by column chromatography using dichloromethane as eluent to give the product as a white solid (2.27 g, 66%); NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 1.40 (t, 3H), 4.42 (q, 2H), 7.25 (m, 1H), 7.40 (m, 1H), 7.55 (m, 1H), 8.20 (m, 1H), 12.77 (s, 1H); *M/z* (+) 218.3 (MH<sup>+</sup>).

## Preparation 15

### Ethyl 3-formyl-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate

Sodium hydride (488 mg, 60% in mineral oil) was added to a stirred solution of ethyl 30 3-formylindole-2-carboxylate (2.21 g) in DMF (100 ml) under argon, and reaction stirred at ambient temperature for 25 minutes. 3,4-Dichlorobenzyl chloride (1.71 ml) was then added and the reaction stirred overnight. The reaction mixture was concentrated *in vacuo* and the

residue dissolved in ethyl acetate (80 ml) and washed with water (2 x 80 ml), dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo* to give a crude residue which was purified by column chromatography using ethyl acetate : *iso*-hexane as eluent (gradient 5/95 - 100/0), to give the product as a yellow solid (2.17g, 57%); NMR d ( $\text{CD}_3\text{SOCD}_3$ ) 1.25 (t, 3H), 4.40 (q, 2H), 5.80 (s, 2H), 7.00 (m, 1H), 7.30 - 7.50 (m, 3H), 7.55 (m, 1H), 7.65 (m, 1H), 8.35 (m, 1H), 10.48 (s, 1H);  $M/z$  (+) 376.4 ( $M\text{H}^+$ ).

### Preparation 16

#### Ethyl N-(3,4-dichlorobenzyl)-2-ethoxycarbonylindole-3-carboxylate

10 A mixture of sodium chlorite (3.39 g) and sodium dihydrogen orthophosphate (4.54 g) in water (50 ml) was added dropwise to a stirred solution of ethyl 3-formyl-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate (1.56 g) and 2-methylbut-2-ene (50 ml) in *tert*-butyl alcohol (100 ml) at ambient temperature and reaction stirred vigorously overnight. The reaction mixture was concentrated *in vacuo* and the residue dissolved in dichloromethane (100 ml), washed with water (100 ml), dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo* to give the product as a yellow solid (1.50 g, 92%); NMR d ( $\text{CD}_3\text{SOCD}_3$ ) 1.20 (t, 3H), 4.30 (q, 2H), 5.50 (s, 2H), 7.00 (m, 1H), 7.25 (m, 2H), 7.42 (m, 1H), 7.58 (m, 2H), 8.00 (m, 1H), 12.68 (s, 1H);  $M/z$  (-) 390.4 ( $M\text{-H}^+$ ).

### Example 1

#### Ethyl N-(3,4-dichlorobenzyl)-3-benzylthioindole-2-carboxylate (Ethyl ester of Compound 5)

Powdered sodium hydroxide (3.2 g) was added in a single portion to a vigorously stirred solution of ethyl 3-benzylthioindole-2-carboxylate (2.48 g), 3,4-dichlorobenzyl chloride (1.71 g) and tetra-*n*-butylammonium hydrogensulphate (0.5 g) in dichloromethane (100 ml). The reaction was stirred for 6 hours then partitioned between 2M HCl and ethyl acetate. Combined organic extracts were dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo* and the residue purified by column chromatography using *iso*-hexane : 5% ethyl acetate as eluent to give the product as a white crystalline solid (2.26 g, 60%); NMR d ( $\text{CD}_3\text{SOCD}_3$ ) 1.32 (t, 3H), 4.00 (s, 2H), 4.25 (q, 2H), 5.60 (s, 2H), 6.78 (d, 1H), 7.04 (m, 2H), 7.10 - 7.38 (m, 8H), 7.80 (d, 1H);  $M/z$  (+) 470 ( $M^+$ ), 426, 424.

**Example 2**

The procedure described in Example 1 above was repeated using the appropriate indole. Thus were obtained the compounds described below.

5 **Ethyl 3-bromo-N-(3,4-dichlorobenzyl)indole-2-carboxylate (precursor to Compound 73)**

98% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 1.26 (t, 3H), 4.30 (q, 2H), 5.79 (s, 2H), 6.89 (d, 1H), 7.25 (s, 1H), 7.33 - 7.46 (m, 2H), 7.50 (d, 1H), 7.57 - 7.68 (m, 2H); *M/z* (+) 430.1 (MH<sup>+</sup>).

10 **Ethyl N-(3,4-dichlorobenzyl)-3-(2,2-dimethyl-1,3-dioxolane-4-ylmethoxy)indole-2-carboxylate (Ethyl ester of Compound 70)**

71% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 1.26 (t, 3H), 1.29 (s, 3H), 1.34 (s, 3H), 3.84 (t, 1H), 4.10 (m, 1H), 4.25 (q, 2H), 4.42 (m, 1H), 5.71 (s, 2H), 6.86 (m, 1H), 7.13 (t, 1H), 7.32 (m, 2H), 7.53 (m, 2H), 7.77 (d, 1H); *M/z* (+) 478.3 (MH<sup>+</sup>).

15 **Ethyl N-(3,4-dichlorobenzyl)-3-[2-(*N*-acetyl-*N*-phenylamino)ethoxy]indole-2-carboxylate (Ethyl ester of Compound 76)**

82% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 1.22 (t, 3H), 3.27 (s, 3H), 3.44 (t, 2H), 4.15 (t, 2H), 4.25 (q, 2H), 5.70 (s, 2H), 6.85 (d, 1H), 7.10 (t, 1H), 7.27 (m, 7H), 7.53 (m, 2H), 7.64 (d, 2H); *M/z* (+) 525.5 (MH<sup>+</sup>).

20 **Ethyl N-(3,4-dichlorobenzyl)-3-(3-furylmethoxy)indole-2-carboxylate (Ethyl ester of Compound 77)**

64% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 1.23 (t, 3H), 4.24 (q, 2H), 5.09 (s, 2H), 5.71 (s, 2H), (s, 1H), 6.83 (d, 1H), 7.10 (t, 1H), 7.29 (m, 2H), 7.51 (t, 2H), 7.65 (m, 3H); *M/z* (+) 444.4 (MH<sup>+</sup>).

25

**Ethyl N-(3,4-dichlorobenzyl)-3-(cyclohex-2-enylmethoxy)indole-2-carboxylate (Ethyl ester of Compound 78)**

83% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 1.24 (t, 3H), 1.42 (m, 1H), 1.91 (m, 2H), 2.04 (m, 3H), 2.19 (m, 1H), 4.10 (m, 2H), 4.25 (q, 2H), 5.68 (s, 2H), 5.70 (s, 2H), 6.84 (d, 1H), 7.13 (t, 1H), 7.32 (m, 2H), 7.52 (m, 2H), 7.74 (d, 1H); *M/z* (+) 458.4 (MH<sup>+</sup>).

Ethyl N-(3,4-dichlorobenzyl)-3-[4-(hydroxymethyl)cyclohexylmethoxy]indole-2-carboxylate (Ethyl ester of Compound 79)

69% yield; NMR d (CDCl<sub>3</sub>) 0.82 - 2.15 (m, 10H), 1.36 (t, 3H), 3.50 (d, 2H), 4.07 (d, 2H), 4.35 (q, 2H), 5.64 (s, 2H), 6.81 (d, 2H), 7.12 (m, 2H), 7.27 (m, 3H), 7.75 (d, 2H); *M/z* (+) 5 490.5 (MH<sup>+</sup>).

Ethyl N-(3,4-dichlorobenzyl)-3-(4-chlorophenethoxy)indole-2-carboxylate (Ethyl ester of Compound 80)

87% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 1.21 (t, 3H), 3.07 (t, 2H), 4.21 (q, 2H), 4.37 (t, 2H), 5.70 (s, 10 2H), 6.84 (d, 1H), 7.07 (t, 1H), 7.31 (m, 6H), 7.51 (t, 3H); *M/z* (+) 504.5 (MH<sup>+</sup>).

Compound 23 ethyl ester

29% yield; NMR d (CDCl<sub>3</sub>) 1.35 (t, 3H), 3.4 (t, 1H), 3.9 - 4.0 (m, 2H), 4.3 - 4.5 (m, 4H), 5.6 (s, 2H), 6.8 (d, 1H), 7.1 - 7.4 (m, 5H), 7.8 (d, 1H); *M/z* (+) 410.3 (MH<sup>+</sup>), 408.2.

15

Compound 26 ethyl ester

45% yield; NMR d (CDCl<sub>3</sub>) 1.35 (t, 3H), 3.2 (t, 2H), 4.3 (q, 2H), 4.45 (t, 2H), 5.65 (s, 2H), 6.8 (dd, 1H), 7.05 - 7.4 (m, 10H), 7.5 (d, 1H); *M/z* (+) 470.3 (MH<sup>+</sup>), 468.4.

20

2-ethyl ester & methyl ester of Compound 27

66% yield; *M/z* (+) 438.3 (MH<sup>+</sup>), 436.2.

Ethyl ester of Compound 66

25 62% yield; NMR d (CDCl<sub>3</sub>) 1.4 (t, 3H), 3.5 (s, 3H), 4.3 - 4.4 (m, 4H), 5.65 (s, 2H), 6.85 (dd, 1H), 7.1 - 7.4 (m, 5H), 7.8 (d, 1H); *M/z* (+) 424 (MH<sup>+</sup>), 422.

Ethyl ester of Compound 67

73% yield; NMR d (CDCl<sub>3</sub>) 1.4 (t, 3H), 1.5 (s, 9H), 3.7 (q, 2H), 4.4 (q, 2H), 5.65 (s, 2H), 6.8 (dd, 1H), 7.1 - 7.4 (m, 5H), 7.9 (d, 1H); *M/z* (+) 507.3 (MH<sup>+</sup>).

Methyl 3-amino-N-(3,4-dichlorobenzyl)indole-2-carboxylate (Precursor to Compound 1, 2)

64% yield; NMR d ( $CD_3SOCD_3$ ) 3.75 (s, 3H), 5.6 (s, 2H), 6.0 (s, 2H), 6.8 - 7.0 (m, 2H), 7.1 - 7.5 (m, 4H), 7.85 (d, 1H);  $M/z$  (+) 351.2 ( $MH^+$ ), 349.2.

5

Di-ethyl ester Compound 24

38% yield; NMR d ( $CDCl_3$ ) 1.05 (t, 3H), 1.4 (t, 3H), 3.6 (s, 2H), 3.95 (q, 2H), 4.4 (q, 2H), 5.7 (s, 2H), 6.85 (dd, 1H), 7.2 - 7.4 (m, 5H), 7.9 (d, 1H);  $M/z$  (+) 468.3 ( $MH^+$ ), 466.3.

10 Ethyl 3-amino-N-(3,4-dichlorobenzyl)indole-2-carboxylate (Precursor to Compound 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22)

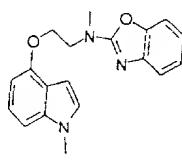
44% yield; NMR d ( $CD_3SOCD_3$ ) 1.21 (t, 3H), 4.21 (q, 2H), 5.56 (s, 2H), 6.00 (s, 2H), 6.86 (d, 1H), 6.98 (t, 1H), 7.22 (d, 1H), 7.30 (t, 1H), 7.40 (d, 1H), 7.48 (d, 1H), 7.86 (d, 1H);  $M/z$  (+) 363 ( $MH^+$ ).

15

Example 3

Ethyl ester of Compound 73

Sodium hydride (23 mg, 60% dispersion in mineral oil) was added in a single portion to a stirred solution of compound of formula (A) (0.19 g) in DMF (3.0 ml) and the reaction 20 stirred for 30 mins.



(A)

3,4-Dichlorobenzyl chloride (0.1 ml) was added and the reaction stirred for 16 hours. The reaction was poured into water and extracted with ethyl acetate. Combined organic extracts 25 were dried ( $MgSO_4$ ) and concentrated and the residue purified by chromatography using *iso*-hexane : 20% ethyl acetate as eluent to give the product as a colourless oil (0.23 g, 85%);  $M/z$  (+) 540, 538 ( $MH^+$ ).

**Example 4**

The procedure described in Example 3 above was repeated using the appropriate indole. Thus were obtained the compounds described below.

**5 Ethyl ester of Compound 74**

93% yield;  $M/z$  (+) 545, 543 ( $MH^+$ ).

**Ethyl ester of Compound 75**

73% yield;  $M/z$  (+) 507, 505 ( $MH^+$ ), 461, 459, 318.

10

**Ethyl N-(3,4-dichlorobenzyl)indole-2-carboxylate**

60% yield;  $M/z$  (+) 349 ( $MH^+$ )

**Diethyl N-(3,4-dichlorobenzyl)-2,3-dicarboxylate**

74% yield;  $M/z$  (+) 392, 394 ( $MH^+$ )

15

**Example 5****Ethyl N-(3,4-dichlorobenzyl)-3-(2-ethoxyethoxy)-5-methoxyindole-2-carboxylate (Ethyl ester of Compound 82)**

To a solution of ethyl *N*-(3,4-dichlorobenzyl)-3-(2-ethoxyethoxy)-5-methoxyindole-2-carboxylate (3.0 g) in DMF (50 ml) was add anhydrous potassium carbonate (3.0 g), 3,4-dichlorobenzyl chloride (2.0 ml) and potassium iodide (100 mg), and the reaction stirred at 60°C for 3 hours. The solvent was evaporated *in vacuo* and the residue partitioned between water (200 ml) and ether (200 ml), the organic layer was dried ( $MgSO_4$ ) and evaporated to give a gum, which was purified by column chromatography using *iso*-hexane : ethyl acetate (4:1) to give the product (2.5 g, 55%); NMR d ( $CDCl_3$ ) 1.25 (t, 3H), 1.38 (t, 3H), 3.62 (q, 2H), 3.80 (t, 2H), 3.86 (s, 3H), 4.3 - 4.4 (m, 4H), 5.62 (s, 2H), 6.80 (dd, 1H), 6.96 (dd, 1H), 7.12 (s, 1H), 7.14 (d, 1H), 7.20 (d, 1H), 7.26 (d, 1H).

**Example 6**

30 The procedure described in Example 5 above was repeated using the appropriate indole and benzyl halide. Thus was obtained the compound described below.

Ethyl N-(3,4-dichlorobenzyl)-3-(2-hydroxethoxy)-5-methoxyindole-2-carboxylate(Ethyl ester of Compound 83)

38% yield; NMR d (CDCl<sub>3</sub>) 1.32 (t, 3H), 3.42 (t, 1H), 3.87 (s, 3H), 3.92 (m, 2H), 4.3 - 4.4 (m, 4H), 5.60 (s, 2H), 6.80 (dd, 1H), 7.02 (dd, 1H), 7.1 - 7.2 (m, 3H), 7.32 (d, 1H); M/z (+) 440 (5) (MH<sup>+</sup>), 438.

Example 7N-(3,4-Dichlorobenzyl)-3-benzylsulphinylinole-2-carboxylic acid (Compound 25)

A solution of ethyl N-(3,4-dichlorobenzyl)-3-benzylthioindole-2-carboxylate (0.50 g)

10 in dichloromethane (2 ml) was added to a slurry of wet alumina (1 g) and Oxone® (0.615 g) in dichloromethane (10 ml). The mixture was then heated at reflux for two hours, and allowed to cool. The product was washed away from the alumina using methylene chloride (200 ml). The solution was then dried (MgSO<sub>4</sub>) and evaporated to afford the crude sulphoxide ester (103 mg). The crude ester was dissolved in THF (2 ml) and methanol (1 ml), and sodium hydroxide 15 (2M, 3 ml) was added. The solution was stirred for five hours, then concentrated *in vacuo*. The residue was dissolved in water (10 ml) and the product precipitated by dropwise addition of aqueous HCl (2M, 10 ml). The resulting solid was collected by filtration and washed with cold water, then dried *in vacuo* to afford the product as a pale yellow solid (36 mg, 7 %. 2 steps), NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 4.37 (d, 2H), 5.83 (d, 2H), 6.96 (dd, 1H), 7.10 (m, 3H), 7.20 (m, 20 3H), 7.30 (t, 1H), 7.38 (d, 1H), 7.59 (s, 1H), 7.62 (s, 1H), 8.05 (d, 1H); M/z (-) 456 (M-H<sup>+</sup>), 412, 365, 323, 323, 321, 320.

Example 8Ethyl N-(3,4-dichlorobenzyl)-3-benzylsulphonylinole-2-carboxylate (Ethyl ester of Compound 21)

25 To a solution of ethyl N-(3,4-dichlorobenzyl)-3-benzylthioindole-2-carboxylate (520 mg) in acetic acid (12 ml) was added hydrogen peroxide solution (30%, 2.5 ml) and the resulting mixture was stirred for 18 hours. The reaction mixture was poured into water (20 ml), made basic with sodium bicarbonate and extracted with dichloromethane. The organic extracts were dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The residue was purified by column 30 chromatography using *iso*-hexane : 20% ethyl acetate as eluent to give the product as a yellow gum (205 mg, 37%); NMR d (CDCl<sub>3</sub>) 1.4 (t, 3H), 4.45 (q, 2H), 4.6 (s, 2H), 5.5 (s, 2H), 6.9 (dd, 1H), 7.1 - 7.3 (m, 9H), 7.4 (d, 1H), 7.7 (d, 1H); M/z (+) 504.3 (MH<sup>+</sup>), 502.4.

**Example 9**

The procedure described in Example 8 above was repeated using the appropriate thioindole. Thus was obtained the compound described below.

5

**Di-ethyl ester of Compound 51**

48% yield;  $M/z$  (+) 500.2 ( $MH^+$ ), 498.3.

**Example 10****10 *N*-(3,4-Dichlorobenzyl)-3-benzylthioindole-2-carboxylic acid (Compound 5)**

Ethyl *N*-(3,4-dichlorobenzyl)-3-benzylthioindole-2-carboxylate (0.31 g) was dissolved in THF / methanol (1:1) and sodium hydroxide (2M, 2.0 ml) was added and the reaction stirred for 16 hours. The reaction was then concentrated *in vacuo* and the residue dissolved in water. The solution was acidified by dropwise addition of acetic acid, resulting in the precipitation of a white solid which was filtered, washed with water and dried *in vacuo* to give the desired end product (0.082 g, 28%); NMR d ( $CD_3SOCD_3$ ) 4.04 (s, 2H), 5.72 (s, 2H), 6.83 - 7.62 (m, 12H);  $M/z$  (-) 442 ( $M^+$ ), 440, 428, 398, 396, 307, 305.

**Example 11**

20 The procedure described in Example 10 above was repeated using the appropriate ester. Thus were obtained the compounds described below.

**Compound 70**

70% yield; NMR d ( $CD_3SOCD_3$ ) 1.30 (s, 3H), 1.35 (s, 3H), 3.87 (m, 1H), 4.10 (m, 3H), 4.40 (m, 1H), 5.75 (s, 2H), 6.90 (d, 2H), 7.13 (t, 1H), 7.32 (m, 2H), 7.51 (m, 2H), 7.75 (d, 2H);  $M/z$  (-) 448.2 ( $M-H^+$ ).

**Compound 76**

85% yield; NMR d ( $CD_3SOCD_3$ ) 3.35 (m, 2H), 3.44 (s, 3H), 5.80 (s, 2H), 7.10 (m, 2H), 7.21 (m, 6H), 7.42 (m, 3H), 7.59 (d, 1H);  $M/z$  (-) 495.4 ( $M-H^+$ ).

**Compound 77**

61% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 5.10 (s, 2H), 5.77 (s, 2H), 6.58 (s, 1H), 6.89 (d, 1H), 7.07 (t, 1H), 7.27 (m, 2H), 7.50 (m, 2H), 7.62 (m, 3H); M/z (-) 414.2 (M-H<sup>+</sup>).

**5 Compound 78**

57% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 1.40 (m, 1H), 2.00 (m, 6H), 4.08 (d, 2H), 5.67 (s, 2H), 5.73 (s, 2H), 6.90 (m, 1H), 7.10 (m, 1H), 7.30 (m, 2H), 7.52 (m, 2H), 7.70 (m, 1H); M/z (-) 428.3 (M-H<sup>+</sup>).

**10 Compound 79**

68% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 0.96 (m, 4H), 1.52 (m, 1H), 1.77 (m, 2H), 1.90 (m, 3H), 3.20 (d, 2H), 3.96 (d, 2H), 5.78 (s, 2H), 7.00 (m, 2H), 7.15 (t, 1H), 7.35 (m, 2H), 7.50 (m, 2H); M/z (-) 460.4 (M-H<sup>+</sup>).

**15 Compound 80**

65% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 2.99 (t, 2H), 4.35 (t, 2H), 5.80 (s, 2H), 6.87 (t, 1H), 7.04 (m, 2H), 7.23 (m, 2H), 7.36 (m, 5H), 7.48 (d, 1H); M/z (-) 474.3 (M-H<sup>+</sup>).

**Compound 71**

20 91% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 3.52 (m, 2H), 3.86 (m, 1H), 4.12 (m, 1H), 4.27 (m, 1H), 5.74 (s, 2H), 6.90 (d, 1H), 7.18 (t, 1H), 7.38 (m, 2H), 7.58 (m, 2H), 7.87 (d, 1H), M/z (-) 408.2 (M-H<sup>+</sup>).

**3-Bromo-N-(3,4-dichlorobenzyl)indole-2-carboxylic acid (precursor to Compound 72)**

25 90% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 5.83 (s, 2H), 6.89 (m, 1H), 7.25 (t, 1H), 7.39 (m, 2H), 7.51 (d, 1H), 7.60 (m, 2H); M/z (-) 398.2 (M-H<sup>+</sup>), 354.3.

**Compound 73**

48% yield; M/z (-) 510 (M<sup>+</sup>), 508, 466, 464.

30

**Compound 74**

21% yield; M/z (-) 515 (M<sup>+</sup>), 513, 425, 143.

**Compound 75**

53% yield;  $M/z$  (-) 477 ( $M^+$ ), 475, 431, 290.

**5 *N*-(3,4-Dichlorobenzyl)-2-carboxylic acid-3-indoleacetic acid (Compound 28)**

92% yield; NMR d ( $CD_3SOCD_3$ ) 3.72 (s, 2H), 5.80 (s, 2H), 7.00 - 7.10 (m, 2H), 7.16 (t, 1H), 7.33 - 7.40 (m, 2H), 7.49 (d, 1H), 7.58 (d, 1H);  $M/z$  (-) 376 ( $M-H^+$ ).

**Compound 68**

10 57% yield; NMR d ( $CD_3SOCD_3$ ) 1.50 - 2.00 (m, 4H), 3.60 (q, 1H), 3.80 (q, 1H), 3.90 (m, 1H), 5.75 (s, 2H), 7.10 (m, 3H), 7.35 (d, 1H), 7.45 (s, 1H), 7.50 (d, 1H), 8.25 (d, 1H);  $M/z$  (-) 445.2 ( $M-H^+$ ).

**Compound 81**

15 93% yield; NMR d ( $CD_3SOCD_3$ ) 2.25 (m, 1H), 3.05 - 3.60 (m, 5H), 4.80 (m, 1H), 5.90 (s, 2H), 7.05 (m, 1H), 7.30 (t, 1H), 7.40 (m, 2H), 7.65 (m, 2H), 7.80 (m, 1H), 8.95 (m, 1H);  $M/z$  (-) 479.4 ( $M-H^+$ ).

**Compound 84**

20 58% yield;  $M/z$  (-) 479.2 ( $M-H^+$ ).

**Compound 85**

81% yield;  $M/z$  (-) 470.2 ( $M-H^+$ ).

**25 (Z)-*N*-(3,4-Dichlorobenzyl)-2-carboxyindole-3-acrylic acid (Compound 50)**

81% yield; NMR d ( $CD_3SOCD_3$ ) 5.80 (s, 2H), 6.50 (d, 1H), 6.90 (m, 1H), 7.30 (m, 3H), 7.50 (d, 1H), 7.60 (m, 1H), 8.00 (m, 1H), 8.40 (d, 1H);  $M/z$  (-) 388.4 ( $M-H^+$ ).

***N*-(3,4-Dichlorobenzyl)-3-(2-ethoxyethoxy)-5-methoxyindole-2-carboxylic acid**

30 (Compound 82)

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14026232

60% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 1.14 (t, 3H), 3.46 (q, 2H), 3.60 (t, 2H), 3.73 (s, 3H), 4.25 (t, 2H), 5.80 (s, 2H), 6.70 (dd, 1H), 6.95 (d, 1H), 7.1 - 7.2 (m, 2H), 7.32 (d, 1H), 7.46 (d, 1H); M/z (-) 438 (M-H<sup>+</sup>), 438.

5 Compound 23

84% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 3.7 (t, 2H), 4.2 (t, 2H), 5.7 (s, 2H), 6.9 (dd, 1H), 7.1 (t, 1H), 7.3 - 7.4 (m, 2H), 7.5 - 7.6 (m, 2H), 7.8 (d, 1H); M/z (-) 380.2 (M<sup>+</sup>), 378.2.

Compound 26

10 87% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 3.1 (t, 2H), 4.35 (t, 2H), 5.7 (s, 2H), 6.9 (dd, 1H), 7.05 (t, 1H), 7.2 - 7.4 (m, 7H), 7.45 - 7.76 (m, 4H); M/z (-) 440.2 (M<sup>+</sup>), 438.1.

Compound 27

94% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 4.6 (s, 2H), 5.7 (s, 2H), 6.95 (dd, 1H), 7.1 (t, 1H), 7.2 (t, 1H), 7.37 (d, 1H), 7.4 - 7.5 (m, 2H), 7.7 (d, 1H); M/z (-) 394 (M<sup>+</sup>), 392.

Compound 66

49% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 3.6 (t, 2H), 4.25 (t, 2H), 5.85 (s, 2H), 6.9 (t, 1H), 7.0 (t, 1H), 7.1 (dd, 1H), 7.25 (d, 1H), 7.4 (s, 1H), 7.5 (d, 2H); M/z (-) 394.2 (M<sup>+</sup>), 392.1.

20

Compound 67

59% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 1.4 (s, 9H), 3.3 (s, 3H), 4.1 (t, 2H), 5.7 (s, 2H), 6.8 - 7.0 (m, 2H), 7.1 (d, 1H), 7.3 - 7.4 (m, 2H), 7.5 (t, 2H), 7.7 (d, 1H); M/z (-) 479.3 (M<sup>+</sup>).

25

Compound 1

84% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 5.9 (s, 2H), 6.95 (dd, 1H), 7.1 (t, 1H), 7.3 - 7.4 (m, 2H), 7.5 - 7.7 (m, 4H), 7.8 (d, 1H), 8.0 (d, 1H), 8.1 (s, 1H); M/z (-) 473.1 (M<sup>+</sup>), 471.1.

30 Compound 2

47% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 5.85 (s, 2H), 6.95 (d, 1H), 7.1 (t, 1H), 7.3 - 7.4 (m, 2H), 7.5 (d, 1H), 7.8 (d, 1H); M/z (-) 413.1 (M<sup>+</sup>), 411.1.

**N-(3,4-Dichlorobenzyl)-3-benzylsulphonylindole-2-carboxylic acid (Compound 21)**

81% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 4.8 (s, 2H), 5.7 (s, 2H), 7.0 - 7.25 (m, 8H), 7.4 - 7.6 (m, 4H); M/z (+) 474.3 (MH<sup>+</sup>).

5

**Compound 24**

98% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 3.6 (s, 2H), 5.75 (s, 2H), 6.9 (dd, 1H), 7.2 - 7.4 (m, 3H), 7.5 (dd, 2H), 7.8 (d, 1H); M/z (-) 410.1 (M<sup>-</sup>), 408.1.

10 **N-(3,4-Dichlorobenzyl)-3-(2-hydroxyethoxy)-5-methoxyindole-2-carboxylic acid (Compound 83)**

93% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 3.46 (t, 2H), 3.74 (s, 3H), 4.14 (t, 2H), 5.80 (s, 2H), 6.63 (dd, 1H), 7.96 (d, 1H), 7.06 (dd, 1H), 7.20 (d, 1H), 7.30 (s, 1H), 7.46 (d, 1H); M/z (-) 410 (M-H<sup>+</sup>), 408.

15

**N-(3,4-Dichlorobenzyl)-3-morpholinosulphonylindole-2-carboxylic acid (Compound 3)**

59% yield; NMR d (CDCl<sub>3</sub>) 3.05 - 3.15 (m, 4H), 3.7 - 3.8 (m, 4H), 5.7 (s, 2H), 6.9 (dd, 1H), 7.2 - 7.5 (m, 5H), 8.2 (d, 1H); M/z (+) 471 (MH<sup>+</sup>), 469.

20 **N-(3,4-Dichlorobenzyl)-3-(1,1-dioxidothiomorpholino)sulphonylindole-2-carboxylic acid (Compound 4)**

93% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>), 3.1 - 3.2 (m, 4H), 3.7 - 3.8 (m, 4H), 5.45 (s, 2H), 7.1 - 7.2 (m, 2H), 7.3 - 7.45 (m, 2H), 7.5 (d, 1H), 7.7 - 7.8 (m, 2H); M/z (+) 519.2 (MH<sup>+</sup>), 517.2.

25 **Compound 51**

23% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>), 4.1 (s, 2H), 5.6 (s, 2H), 7.1 (m, 2H), 7.3 - 7.4 (m, 2H), 7.5 (d, 1H), 7.7 (s, 1H), 7.9 (m, 1H); M/z (-) 442 (M<sup>-</sup>), 440.

**Compound 86**

27% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 6.65 (s, 2H), 7.45 (dd, 1H), 7.6-7.75 (m, 2H), 7.8 (d, 1H), 7.95 (t, 1H), 8.95 (d, 1H); M/z (-) 362, 364 (M<sup>+</sup>)

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Example 12Ethyl N-(3,4-dichlorobenzyl)-3-morpholinosulphonylindole-2-carboxylate [Ethyl ester of Compound 3]

To a suspension of ethyl *N*-(3,4-dichlorobenzyl)-3-morpholinosulphonylindole-2-carboxylate (803 mg) in acetone (40 ml) was added a solution of potassium permanganate (528 mg) in water (15 ml). The resulting mixture was stirred for 18 hours. The mixture was poured into water (20 ml) and extracted with diethyl ether, dried ( $\text{MgSO}_4$ ) and concentrated to a gum which was purified by column chromatography using *iso*-hexane : ethyl acetate (3:1) as eluent to give the desired product (681 mg, 82%); NMR d ( $\text{CDCl}_3$ ) 1.3 (t, 3H), 3.2 - 3.2 (m, 10 4H), 3.7 - 3.8 (m, 4H), 5.4 (s, 2H), 6.95 (d, 1H), 7.3 - 7.4 (m, 5H), 8.05 (d, 1H);  $M/z$  (+) 499.2 ( $\text{MH}^+$ ), 497.3.

Example 13

The procedure described above in Example 12 was repeated using the appropriate 15 amine. Thus was obtained the compound described below.

Ethyl N-(3,4-dichlorobenzyl)-3-(1,1-dioxidothiomorpholino)sulphonylindole-2-carboxylate [Ethyl ester Compound 4]

49% yield; NMR d ( $\text{CDCl}_3$ ) 1.3 (t, 3H), 3.1 - 3.2 (m, 4H), 3.9 - 4.0 (m, 4H), 4.4 (q, 2H), 5.4 20 (s, 2H), 6.9 (dd, 1H), 7.2 - 7.4 (m, 5H), 8.0 (d, 1H);  $M/z$  (-) 545.2 ( $M'$ ), 543.1.

Example 14Compound 6

*N*-(3,4-Dichlorobenzyl)-2-ethoxycarbonylindole-3-sulphonyl chloride (0.12 g), *N*-25 methylpiperazine (0.15 ml), triethylamine (0.19 ml) and 4-dimethylaminopyridine (30 mg) were stirred for 4 hours in dichloromethane (2.0 ml). The reaction was washed with water, dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo*. The residue was dissolved in THF / methanol (1:1) and sodium hydroxide (3M, 1.0 ml) was added and the reaction stirred for 16 hours. The reaction was then concentrated *in vacuo* and the residue dissolved in water. The solution was 30 acidified by dropwise addition of acetic acid, resulting in the precipitation of a white solid which was filtered, washed with water and dried *in vacuo* to give the desired end product (61 mg, 47%, 2 steps); NMR d ( $\text{CD}_3\text{SOCD}_3$ ) 2.57 (s, 3H), 3.00 (m, 4H), 3.32 (m, 4H), 5.37 (s,

2H), 7.19 (m, 2H), 7.28 (d, 1H), 7.43 (m, 2H), 7.65 (s, 1H), 7.80 (m, 1H);  $M/z$  (+) 482 ( $M^+$ ), 236, 215, 196, 159, 142.

### Example 15

5 The procedure described in Example 14 above was repeated using the appropriate amines. Thus were obtained the compounds described below.

#### Compound 7

57% yield (2 steps); NMR d ( $CD_3SOCD_3$ ) 2.63 (s, 6H), 3.10 (m, 4H), 5.68 (s, 2H), 7.12 - 7.26 10 (m, 3H), 7.44 - 7.60 (m, 3H), 7.96 (m, 1H), 8.37 (t, 1H);  $M/z$  (+) 470 ( $M^+$ ), 214, 158, 141, 123.

#### Compound 29

61% yield (2 steps);  $M/z$  (-) 457 ( $M^+$ ), 455, 413, 411.

15

#### Compound 30

30% yield (2 steps);  $M/z$  (-) 487 ( $M^+$ ), 485, 443, 441, 399, 397, 355, 353.

#### Compound 31

20 23% yield (2 steps);  $M/z$  (-) 492 ( $M-H^+$ ), 449, 420, 400, 398, 354, 308, 222.

#### Compound 32

45% yield (2 steps);  $M/z$  (-) 497 ( $M^+$ ), 495, 453, 451.

25 Compound 33

44% yield (2 steps);  $M/z$  (-) 436 ( $M-CO_2^+$ ), 434.

#### Compound 34

30 40% yield (2 steps);  $M/z$  (-) 493 ( $M^+$ ), 449, 447, 340, 338.

**Compound 35**

49% yield (2 steps);  $M/z$  (-) 512 ( $M^+$ ), 510, 468, 466.

**Compound 36**

5 60% yield (2 steps);  $M/z$  (-) 512 ( $M^+$ ), 510, 468, 466.

**Compound 37**

52% yield (2 steps);  $M/z$  (-) 446 ( $M\text{-CO}_2^+$ ), 444.

**Compound 38**

43% yield (2 steps);  $M/z$  (-) 443 ( $M\text{-CO}_2^+$ ), 441.

**Compound 39**

29% yield (2 steps);  $M/z$  (-) 393 ( $M\text{-CO}_2^+$ ), 391.

**Compound 40**

54% yield (2 steps);  $M/z$  (-) 515 ( $M^+$ ), 513, 471, 469.

**Compound 41**

20 34% yield (2 steps);  $M/z$  (-) 465 ( $M\text{-CO}_2^+$ ), 463.

**Compound 42**

20% yield (2 steps);  $M/z$  (-) 473 ( $M\text{-CO}_2^+$ ), 369, 367.

**Compound 43**

37% yield (2 steps);  $M/z$  (-) 425 ( $M\text{-CO}_2^+$ ), 423.

**Compound 44**

5% yield (2 steps);  $M/z$  (-) 529 ( $M^+$ ), 527, 485, 483, 355, 353, 274.

**Compound 45**

17% yield (2 steps);  $M/z$  (-) 4663 ( $M^+$ ), 464, 422, 420.

Compound 46

6% yield (2 steps);  $M/z$  (-) 451 ( $M\text{-CO}_2^+$ ), 449, 409, 355, 296, 221.

Compound 47

5 22% yield (2 steps);  $M/z$  (-) 549 ( $M^+$ ), 547, 505, 503, 458, 381, 379, 355, 353.

Example 16Ethyl 3-(2,2-dimethyl-1,3-dioxolane-4-ylmethoxy)indole-2-carboxylate (Precursor to Compounds 70 and 71)

10 Rhodium acetate dimer (30 mg) was added to a solution of solketal (0.87 ml) and ethyl 3-diazoindole-2-carboxylate (300 mg) in dichloroethane (10 ml), and stirred at 85°C for 3 hours. The reaction was concentrated *in vacuo* and the residue purified by column chromatography using a gradient of 0% to 20% ethyl acetate : *iso*-hexane as eluent to afford the product as a pale yellow solid (435 mg, 97%); NMR d ( $CD_3SOCD_3$ ) 1.27 - 1.38 (m, 9H), 15 3.88 (m, 1H), 4.11 (m, 3H), 4.30 (q, 2H), (m, 1H), 7.01 (t, 1H), 7.24 (t, 1H), 7.36 (d, 1H), 7.65 (d, 1H), 11.27 (s, 1H);  $M/z$  (+) 320.3 ( $MH^+$ ).

Example 17

The procedure described in Example 16 above was repeated using the appropriate 20 diazoindole and alcohols. Thus were obtained the compounds described below.

Ethyl 3-[2-(*N*-acetyl-*N*-phenylamino)ethoxy]indole-2-carboxylate (Precursor to Compound 76)

75% yield; NMR d ( $CD_3SOCD_3$ ) 1.32 (t, 3H), 3.41 (m, 5H), 4.12 (t, 2H), 4.31 (q, 2H), 6.99 (t, 25 1H), 7.23 (m, 6H), 7.36 (d, 1H), 7.58 (d, 1H), 11.28 (s, 1H);  $M/z$  (+) 367.4 ( $MH^+$ ).

Ethyl 3-(3-furylmethoxy)indole-2-carboxylate (Precursor to Compound 77)

47% yield; NMR d ( $CD_3SOCD_3$ ) 1.31 (t, 3H), 4.31 (q, 2H), 5.07 (s, 2H), 6.57 (s, 1H), 6.99 (t, 1H), 7.21 (t, 1H), 7.36 (d, 1H), 7.60 (m, 3H);  $M/z$  (+) 286.3 ( $MH^+$ ).

Ethyl 3-(cyclohex-2-enylmethoxy)indole-2-carboxylate (Precursor to Compound 78)

90% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 1.31 (t, 3H), 1.39 (m, 1H), 1.80 - 2.30 (m, 6H), 4.08 (m, 2H), 4.30 (q, 2H), 5.66 s, 2H), 7.01 (t, 1H), 7.22 (t, 1H), 7.35 (d, 1H), 7.62 (d, 1H), 11.19 (s, 1H); M/z (+) 300.3 (MH<sup>+</sup>).

5

Ethyl 3-[4-(hydroxymethyl)cyclohexylmethoxy]indole-2-carboxylate (Precursor to Compound 79)

72% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 0.80 - 2.00 (m, 10H), 1.32 (t, 3H), 3.21 (m, 2H), 4.00 (d, 2H), 4.30 (q, 2H), 7.00 (t, 1H), 7.22 (t, 1H), 7.35 (d, 1H), 7.61 (d, 1H), 10 11.18 (s, 1H); M/z (+) 332.4 (MH<sup>+</sup>).

Ethyl 3-(4-chlorophenethyloxy)indole-2-carboxylate (Precursor to Compound 80)

81% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 1.30 (t, 3H), 3.03 (t, 2H), 4.27 (q, 2H), 4.36 (t, 2H), 6.97 (t, 1H), 7.15 - 7.45 (m, 7H), 11.22 (s, 1H); M/z (+) 344.3 (MH<sup>+</sup>).

Precursor to Compd No	Structure	Yield/Properties
73		47% yield; M/z (+) 380 (MH <sup>+</sup> ).
74		45% yield; M/z (+) 385 (MH <sup>+</sup> ).
75		53% yield; M/z (+) 347 (MH <sup>+</sup> ), 301.

82		95% yield; NMR d (CDCl <sub>3</sub> ) 1.24 (t, 3H), 1.42 (t, 3H), 3.60 (q, 2H), 3.80 (t, 2H), 3.85 (s, 3H), 4.38 (t, 2H), 4.42 (q, 2H), 6.96 (dd, 1H), 7.12 (d, 1H), 7.20 (d, 1H), 8.65 (s, 1H); M/z (+) 308 (MH <sup>+</sup> )
83		65% yield; NMR d (CD <sub>3</sub> SOCD <sub>3</sub> ) 1.33 (t, 3H), 3.70 (q, 2H), 3.78 (s, 3H), 4.15 (t, 2H), 4.32 (q, 2H), 4.76 (t, 1H), 6.90 (dd, 1H), 7.08 (d, 1H), 7.26 (d, 1H); M/z (+) 280 (MH <sup>+</sup> )
23		80% yield; NMR d (CDCl <sub>3</sub> ) 1.4 (t, 3H), 3.65 (t, 1H), 3.8 - 3.9 (m, 2H), 4.4 - 4.5 (m, 4H), 7.05 - 7.1 (m, 1H), 7.35 (d, 2H), 7.7 (d, 1H), 8.3 (brs, 1H); M/z (+) 250.3 (MH <sup>+</sup> )
26		92% yield; NMR d (CDCl <sub>3</sub> ) 1.4 (t, 3H), 3.1 (t, 1H), 4.4 (q, 2H), 4.45 (t, 2H), 7.0 - 7.1 (m, 1H), 7.2 - 7.3 (m, 7H), 7.5 (d, 1H), 8.35 (bs, 1H); M/z (+) 310.3 (MH <sup>+</sup> )
27		58% yield; NMR d (CDCl <sub>3</sub> ) 1.4 (t, 3H), 3.8 (s, 3H), 4.4 (q, 2H), 4.9 (s, 2H), 7.1 - 7.15 (m, 1H), 7.3 - 7.4 (m, 2H), 7.8 (d, 1H), 8.4 (brs, 1H); M/z (+) 278.3 (MH <sup>+</sup> )
66		94% yield; NMR d (CDCl <sub>3</sub> ) 1.4 (t, 3H), 3.5 (s, 3H), 3.75 (t, 2H), 4.4 - 4.5 (m, 4H), 7.1 - 7.2 (m, 2H), 7.3 (d, 2H), 7.8 (d, 1H), 8.4 (brs, 1H); M/z (+) 264.4 (MH <sup>+</sup> )

67		70% yield; NMR d (CDCl <sub>3</sub> ) 1.4 - 1.5 (m, 12H), 3.5 - 3.6 (m, 2H), 4.35 (t, 2H), 4.5 (q, 2H), 5.65 (brs, 1H), 7.1 - 7.2 (m, 1H), 7.5 - 7.55 (m, 2H), 7.7 (d, 1H), 8.4 (brs, 1H); M/z (+) 349.4 (MH <sup>+</sup> ).
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### Example 18

#### Compound 69

5 To a suspension of ethyl N-(3,4-dichlorobenzyl)-3-[2-(*t*-butyloxycarbonylamino)-ethoxy]indole-2-carboxylate (112 mg) in ethyl acetate (5 ml) was added a saturated solution of HCl in dioxane (2 ml). The mixture was stirred for 18 hours and the resulting solid filtered and dried *in vacuo* (26 mg, 50%); NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 2.4 - 2.5 (m, 2H), 4.3 - 4.4 (m, 2H), 6.9 (d, 1H), 7.1 - 7.6 (m, 4H), 7.8 (d, 1H), 8.1 (brs, 2H); M/z (-) 379 (M<sup>+</sup>), 377.

10

### Example 19

#### Ethyl N-(3,4-dichlorobenzyl)-3-(2,3-dihydroxypropoxy)indole-2-carboxylate (Ethyl ester of Compound 71)

15 Ethyl N-(3,4-dichlorobenzyl)-3-(2,2-dimethyl-1,3-dioxolane-4-ylmethoxy)-indole-2-carboxylate [Compound 70] (15.92 g) was dissolved in tetrahydrofuran (70 ml) and hydrochloric acid (4M, 33 ml), and stirred at ambient temperature for 4 hours. The reaction was concentrated *in vacuo*, added to water (200 ml) and extracted with ethyl acetate (3 x 200 ml). The combined organic extracts were dried (MgSO<sub>4</sub>), and concentrated *in vacuo*, and the residue purified by column chromatography using 70% ethyl acetate : *iso*-hexane as eluent, to afford the product as a dark yellow oil that crystallised upon standing to off white crystals (9.37 g, 65%); NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 1.27 (t, 3H), 3.50 (m, 2H), 3.83 (m, 1H), 4.08 (m, 1H), 4.20 (m, 1H), 4.27 (q, 2H), 4.58 (t, 1H), 4.88 (d, 1H), 5.73 (s, 2H), 6.88 (d, 1H), 7.15 (t, 1H), 7.33 (m, 2H), 7.54 (m, 2H), 7.82 (d, 1H), M/z (+) 438.3 (MH<sup>+</sup>).

**Example 20****t-Butyl N-(3,4-dichlorobenzyl)-3-morpholinoindole-2-carboxylate (t-butyl ester of Compound 72)**

5  $Pd_2(dbu)_3$  (114 mg), *R*-BINAP (69 mg), potassium *t*-butoxide (294 mg), and morpholine (0.209 ml) were added to a solution of *t*-butyl 3-bromo-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate (1 g) in de-gassed toluene (6 ml), under an atmosphere of argon. The reaction was stirred and heated at 90°C for 16 hours then poured into water (50 ml), extracted with ethyl acetate (3 x 50 ml), and the combined organic extracts were dried ( $MgSO_4$ ) and concentrated *in vacuo*. The residue was purified by column chromatography 10 using 10% ethyl acetate : *iso*-hexane as eluent, to afford the product as a yellow oil (325 mg, 33%); NMR d ( $CD_3SOCD_3$ ) 3.20 (t, 4H), 3.73 (t, 4H), 5.56 (s, 2H), 6.88 (d, 1H), 7.7 (t, 1H), 7.25 (m, 2H), 7.50 (m, 2H), 7.80 (d, 1H), *M/z* (+) 461 ( $MH^+$ ), 405.

**Example 21****15 *N*-(3,4-Dichlorobenzyl)-3-morpholinoindole-2-carboxylic acid (Compound 72)**

Trifluoroacetic acid (5 ml) was added to a solution of *t*-butyl *N*-(3,4-dichlorobenzyl)-3-morpholinoindole-2-carboxylate (293 mg) in dichloromethane (10 ml) and the reaction stirred at ambient temperature overnight. The reaction was concentrated *in vacuo* and the residue purified by column chromatography using 20% ethyl acetate : *iso*-hexane as eluent to 20 afford the product as a brown solid (125 mg, 30%); NMR d ( $CD_3SOCD_3$ ) 3.10 (t, 4H), 3.83 (t, 4H), 5.36 (s, 2H), 7.01 (t, 1H), 7.12 (m, 2H), 7.46 (m, 2H), 7.58 (m, 2H), *M/z*(-) 404.2 ( $M-H^+$ ).

**Example 22****25 Compound 48**

Acetic anhydride (0.4 g) was added to a stirred solution of *N*-(3,4-dichlorobenzyl)-2-carboxy-3-indoleacetic acid (0.1 g) in dry DCM (5 mls) under an inert atmosphere and heated to 50°C for 4 hours. The reaction was cooled, concentrated *in vacuo* and toluene added before reducing *in vacuo* again. The resultant yellow solid was dissolved in DCM under an inert 30 atmosphere before morpholine (0.6 mls) was added and the reaction was stirred for 48 hours at ambient temperature. Combined organic extracts were washed with aqueous hydrochloric acid (2.0 M, 5 ml), water and saturated aqueous sodium chloride solution before concentration

in *vacuo*. The residue was dissolved in saturated aqueous sodium hydrogen orthophosphate and acidified by the addition of aqueous hydrochloric acid (2.0 M, 5 ml) causing the precipitation of the product as a light brown solid. (0.098 g, 83%); NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 3.51 (brs, 2H), 3.60 (M, 4H), 3.71 (brs, 2H), 4.23 (s, 2H), 5.88 (s, 2H), 6.99 (d, 1H), 7.19 (t, 1H), 5 7.32 - 7.40 (m, 2H), 7.56 - 7.63 (m, 2H), 7.78 (d, 1H); *M/z* (-) 445 (*M-H*<sup>+</sup>).

**Example 23**

The procedure described in Example 22 above was repeated using the appropriate amines. Thus were obtained the compounds described below.

10

**Compound 49**

69% yield; NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 3.11 (dd, 2H), 3.38 (t, 2H), 3.96 (s, 2H), 5.78 (s, 2H), 6.91 (dd, 1H), 7.12 (t, 1H), 7.24 - 7.35 (m, 2H), 7.44 - 7.53 (m, 2H), 7.72 (d, 1H), 8.02 (M, 1H); *M/z* (-) 419 (*M-H*<sup>+</sup>).

15

**Compound 52**

44% yield; *M/z* (-) 433 (*M-H*<sup>+</sup>).

**Compound 53**

20 32% yield; *M/z* (-) 469 (*M-H*<sup>+</sup>).

**Compound 54**

69% yield; *M/z* (-) 486 (*M-H*<sup>+</sup>).

25 **Compound 55**

42% yield; *M/z* (-) 491 (*M-H*<sup>+</sup>).

**Compound 56**

38% yield; *M/z* (-) 433 (*M-H*<sup>+</sup>).

30

**Compound 57**

58% yield; *M/z* (-) 459 (*M-H*<sup>+</sup>).

**Compound 58**

12% yield;  $M/z$  (-) 544 ( $M-H^+$ ).

**5 Compound 59**

52% yield;  $M/z$  (-) 459 ( $M-H^+$ ).

**Compound 60**

21% yield;  $M/z$  (-) 515 ( $M-H^+$ ).

10

**Compound 61**

25% yield;  $M/z$  (-) 558 ( $M-H^+$ ).

**Compound 62**

15 18% yield;  $M/z$  (-) 489 ( $M-H^+$ ).

**Compound 63**

19% yield;  $M/z$  (-) 509 ( $M-H^+$ ).

**20 Compound 64**

10% yield;  $M/z$  (-) 495 ( $M-H^+$ ).

**Compound 65**

18% yield;  $M/z$  (-) 469 ( $M-H^+$ ).

25

**Example 24****Compound 8**

3,5-Dimethylisoxazole-4-sulphonyl chloride (0.097g) in dichloromethane (2 ml) was added to a stirred solution of ethyl 3-amino-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate (0.15 g) in dichloromethane (3 ml). Pyridine (0.036 g) was added and the reaction was stirred for 16 hours at ambient temperature. The reaction mixture was washed with aqueous citric acid (1.0M, 4 ml), saturated aqueous sodium hydrogencarbonate solution and water and

concentrated *in vacuo*. The residue was dissolved in THF (5 ml) and LiOH (2M, 3 ml) added and the reaction stirred for 16 hours. The reaction was then concentrated *in vacuo* and the residue dissolved in water. The solution was acidified by dropwise addition of acetic acid, resulting in the precipitation of a white solid which was filtered, washed with water and dried 5 *in vacuo* to give the desired end product as a white solid. (75 mg, 37%, 2 steps); NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 2.00 (s, 3H), 2.07 (s, 3H), 5.74 (s, 2H), 6.93 (dd, 1H), 7.17 (t, 1H), 7.24 (d, 1H), 7.34 (t, 1H), 7.55 (dd, 2H), 7.66 (d, 1H), 9.72 (brs, 1H); *M/z* (-) 492 (*M-H*<sup>+</sup>).

### Example 25

10 The procedure described in Example 24 above was repeated using the appropriate acid chloride. Thus were obtained the compounds described below.

#### Compound 9

48% yield (2 steps); NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 2.00 (s, 3H), 2.14 (s, 3H), 5.71 (s, 2H), 6.77 (d, 1H), 7.12 (t, 1H), 7.26 - 7.37 (m, 2H), 7.45 (d, 1H), 7.52 (d, 1H), 7.63 (d, 1H), 9.58 (brs, 1H), 12.39 (s, 1H); *M/z* (-) 551 (*M-H*<sup>+</sup>).

#### Compound 10

66% yield (2 steps); NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 3.56 (s, 3H), 5.71 (s, 2H), 6.82 (dd, 1H), 7.07 (t, 1H), 7.21 - 7.30 (m, 2H), 7.45 - 7.55 (m, 3H), 7.66 - 7.73 (m, 2H), 9.10 (s, 1H); *M/z* (-) 477 (*M-H*<sup>+</sup>).

#### Compound 11

69% yield (2 steps); NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 4.10 (s, 2H), 5.79 (s, 2H), 6.93 (dd, 1H), 7.18 (t, 1H), 7.29 - 7.36 (m, 2H), 7.50 - 7.59 (m, 2H), 7.81 (d, 1H); *M/z* (-) 455 (*M-H*<sup>+</sup>).

#### Compound 12

14% yield (2 steps); NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 1.94 (s, 3H), 3.61 (s, 3H), 5.70 (s, 2H), 6.84 (dd, 1H), 7.12 (t, 1H), 7.27 - 7.34 (m, 2H), 7.52 (t, 2H), 7.61 (d, 1H), 9.28 (brs, 1H); *M/z* (-) 525, 30 527, 529 (*M-H*<sup>+</sup>).

**Compound 13**

79% yield (2 steps); NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 3.49 (s, 3H), 5.68 (s, 2H), 6.79 (dd, 1H), 7.13 (t, 1H), 7.19 (d, 1H), 7.30 (t, 1H), 7.50 - 7.56 (m, 2H), 7.59 - 7.77 (m, 3H), 7.91 (t, 1H), 8.23 (d, 1H), 8.87 (brs, 1H); *M/z* (-) 551 (*M-H<sup>+</sup>*).

5

**Compound 14**

36% yield (2 steps); NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 3.46 (s, 2H), 5.79 (s, 2H), 6.91 (dd, 1H), 7.09 (t, 1H), 7.25 - 7.35 (m, 2H), 7.50 - 7.58 (m, 2H), 7.62 (d, 1H), 9.89 (brs, 1H).

**Compound 15**

90% yield (2 steps); NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 2.10 (s, 3H), 2.67 (m, 2H), 2.76 (m, 2H), 5.79 (s, 2H), 6.92 (dd, 1H), 7.10 (t, 1H), 7.28 - 7.33 (m, 2H), 7.50 - 7.56 (m, 2H), 7.61 (d, 1H), 9.67 (s, 1H); *M/z* (-) 435 (*M-H<sup>+</sup>*).

**Compound 16**

73% yield (2 steps); NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 3.96 (s, 2H), 5.79 (s, 2H), 6.90 (s, 1H), 6.94 - 7.13 (m, 3H), 7.26 - 7.34 (m, 3H), 7.38 (d, 1H), 7.48 - 7.59 (m, 3H), 9.86 (s, 1H), 13.36 (brs, 1H); *M/z* (-) 457 (*M-H<sup>+</sup>*).

**Compound 17**

53% yield (2 steps); NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 1.36 (d, 3H), 4.20 (m, 1H), 5.79 (s, 2H), 6.00 (d, 1H), 6.88 (dd, 1H), 7.07 (t, 1H), 7.28 - 7.35 (m, 2H), 7.50 - 7.56 (m, 2H), 7.99 (d, 1H), 10.21 (brs, 1H); *M/z* (-) 405 (*M-H<sup>+</sup>*).

**Compound 18**

73% yield (2 steps); NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 3.83 (s, 6H), 5.81 (s, 2H), 6.95 (dd, 1H), 7.06 - 7.17 (m, 2H), 7.30 - 7.37 (m, 2H), 7.51 - 7.61 (m, 3H), 7.66 (dd, 1H), 7.75 (d, 1H), 10.08 (brs, 1H); *M/z* (-) 497 (*M-H<sup>+</sup>*).

**Compound 19**

66% yield (2 steps); NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 2.04 (s, 3H), 5.68 (s, 2H), 6.60 (dd, 1H), 7.12 (d, 1H), 7.20 (d, 1H), 7.28 (t, 1H), 7.40 (d, 2H), 7.47 (d, 2H), 7.62 (d, 2H), 7.72 (d, 1H), 9.13 (s, 1H), 10.27 (s, 1H); *M/z* (-) 530 (*M*-H<sup>+</sup>).

5

**Compound 20**

47% yield (2 steps); NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 5.78 (s, 2H), 6.86 (dd, 1H), 7.10 - 7.18 (m, 3H), 7.21 (d, 1H), 7.31 (t, 1H), 7.54 (dd, 1H), 7.63 (d, 1H), 9.80 (brs, 1H); *M/z* (-) 517 (*M*-H<sup>+</sup>), 515, 513.

10

**Compound 22**

40% yield (2 steps); NMR d (CD<sub>3</sub>SOCD<sub>3</sub>) 4.69 (s, 2H), 5.76 (s, 2H), 6.84 (dd, 1H), 7.14 (t, 1H), 7.23 - 7.40 (m, 3H), 7.46 - 7.67 (m, 3H), 7.85 (d, 1H), 10.13 (brs, 1H); *M/z* (-) 546 (*M*-H<sup>+</sup>).

15

**Example 26****Methyl ester of Compound 1**

To a solution of methyl 3-amino-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate (253 mg) in tetrahydrofuran (8 ml) was added triethylamine (0.15 ml) followed by a solution of 3-chlorobenzoyl chloride (153 mg) in tetrahydrofuran (2 ml). The resulting mixture was stirred at room temperature for 4 hours. The mixture was partitioned between water (10 ml) and ethyl acetate (20 ml). The organic layer was dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The residue was purified by column chromatography using *iso*-hexane : 20% ethyl acetate as eluent to give the product (259 mg, 74%); NMR d (CDCl<sub>3</sub>) 3.9 (s, 3H), 5.7 (s, 2H), 6.8 (d, 1H), 7.2 - 7.6 (m, 7H), 7.9 (d, 1H), 8.05 (s, 1H), 8.3 (d, 1H), 10.1 (brs, 1H); *M/z* (-) 487.1 (*M*), 485.0.

**Example 27**

The procedure described in Example 26 above was repeated using the appropriate acid chloride. Thus was obtained the compound described below.

30

**Methyl ester of Compound 2**

37% yield; NMR d (CDCl<sub>3</sub>) 2.95 (s, 3H), 3.95 (s, 3H), 5.7 (s, 2H), 6.8 (dd, 1H), 7.1 - 7.5 (m, 4H), 7.7 (s, 1H), 8.15 (d, 1H); *M/z* (-) 427.3 (*M*<sup>+</sup>), 425.3.

**5 Example 28****Ethyl N-(3,4-dichlorobenzyl)-3-(tetrahydrofurylcarbamoyl)indole-2-carboxylate****(Ethyl ester of Compound 68)**

To a stirred solution of ethyl *N*-(3,4-dichlorobenzyl)-2-ethoxycarbonylindole-3-carboxylic acid (100 mg) in dichloromethane (4 ml) at ambient temperature, under argon, was 10 added DMF (1 drop) and oxalyl chloride in dichloromethane (2M, 153  $\mu$ l). The reaction was stirred at ambient temperature for 7 hours, then concentrated *in vacuo* and dissolved in dichloromethane (4 ml). Tetrahydrofurylamine (53  $\mu$ l) was added, followed by triethylamine (71  $\mu$ l) and the reaction stirred under argon for 16 hours. The reaction was diluted with dichloromethane (30 ml), washed with HCl (2M, 30 ml) and water (30 ml), dried 15 (MgSO<sub>4</sub>) and concentrated *in vacuo* to give a crude residue which was purified by column chromatography, using ethyl acetate : *iso*-hexane as eluent (gradient 10/90 - 50/50), to give the product as an off-white solid (57 mg, 47%); *M/z* (+) 475.3 (*MH*<sup>+</sup>).

**Example 29****20 Ethyl N-(3,4-dichlorobenzyl)-3-(1,1-dioxidotetrahydrothiophene-3-carbamoyl)indole-2-carboxylate (Ethyl ester of Compound 81)**

Ethyl *N*-(3,4-dichlorobenzyl)-2-ethoxycarbonylindole-3-carboxylic acid (104 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (76 mg), 3-aminotetrahydrothiophene 1,1-dioxide (36 mg) and 4-dimethylaminopyridine (5 mg) in 25 dichloromethane (10 ml) were stirred at ambient temperature under argon for 16 hours. The crude reaction mixture was purified by column chromatography using ethyl acetate : *iso*-hexane as eluent (gradient 0/100 - 75/25), to give the product as a white solid (32 mg, 24%); *M/z* (+) 509.4 (*MH*<sup>+</sup>).

**30 Example 30**

The procedure described in Example 29 above was repeated using the appropriate amines. Thus were obtained the compounds described below.

Ethyl N-(3,4-dichlorobenzyl)-3-(1,1-dioxidothiomorpholinocarbonyl)indole-2-carboxylate (Ethyl ester of Compound 84)

48% yield;  $M/z$  (+) 509.1 ( $MH^+$ ).

5

Ethyl N-(3,4-dichlorobenzyl)-3-(3,5-dimethylisoxazol-4-ylmethylcarbamoyl)indole-2-carboxylate (Ethyl ester of Compound 85)

40% yield;  $M/z$  (+) 500.1 ( $MH^+$ ).

10

Example 31

Ethyl (Z)-N-(3,4-dichlorobenzyl)-2-ethoxycarbonylindole-3-acrylic acid (Ethyl ester of Compound 50)

Malonic acid (106 mg) and piperidine (1 drop) were added to a solution of ethyl 3-formyl-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate (315 mg) in pyridine (5 ml) and the reaction stirred at 100°C overnight. The reaction was concentrated *in vacuo* and the residue dissolved in ethyl acetate (30 ml), washed with HCl (2M, 30 ml) and water (30 ml), dried ( $MgSO_4$ ) and concentrated *in vacuo* to give the crude product which was triturated with a mixture of dichloromethane, ethyl acetate and hexane to give the product as a tan coloured solid (68 mg, 19%); NMR d ( $CD_3SOCD_3$ ) 1.25 (t, 3H), 4.35 (q, 2H), 5.80 (s, 2H), 6.55 (d, 1H), 6.90 (m, 1H), 7.25 - 7.45 (m, 3H), 7.50 (m, 1H), 7.60 (m, 1H), 8.05 (m, 1H), 8.35 (d, 1H) 12.24 (s, 1H);  $M/(-)$  416.4 ( $M-H^+$ ).

Example 32

25 Biological Assays for hMCP-1 Antagonists

The following biological test methods, data and Examples serve to illustrate the present invention.

Abbreviations:

ATCC American Type Culture Collection, Rockville, USA.

BCA Bicinchoninic acid, (used, with copper sulphate, to assay protein )

BSA Bovine Serum Albumin

DMEM Dulbecco's modified Eagle's medium

EGTA	Ethylenbis(oxyethylenenitrilo)tetraacetic acid
FCS	Foetal calf serum
HEPES	(N-[2-Hydroxyethyl]piperazine-N'-(2-ethanesulphonic acid])
HBSS	Hank's Balanced Salt Solution
hMCP-1	Human Monocyte Chemoattractant Protein-1
PBS	Phosphate buffered saline
PCR	Polymerase chain reaction

AMPLITAQ™, available from Perkin-Elmer Cetus, is used as the source of thermostable DNA polymerase.

Binding Buffer is 50 mM HEPES, 1 mM CaCl<sub>2</sub>, 5 mM MgCl<sub>2</sub>, 0.5% foetal calf serum, adjusted to pH 7.2 with 1 M NaOH.

5 Non-Essential Amino Acids (100X concentrate) is: L-Alanine, 890 mg/l; L-Asparagine, 1320 mg/l; L-Aspartic acid, 1330 mg/l; L-Glutamic acid, 1470 mg/l; Glycine, 750 mg/l; L-Proline, 1150 mg/l and; L-Serine, 1050 mg/l.

Hypoxanthine and Thymidine Supplement (50x concentrate) is: hypoxanthine, 680 mg/l and; thymidine, 194 mg/l.

10 Penicillin-Streptomycin is: Penicillin G (sodium salt); 5000 units/ml; Streptomycin sulphate, 5000 µg/ml.

Human monocytic cell line THP-1 cells are available from ATCC, accession number ATCC TIB-202.

Hank's Balanced Salt Solution (HBSS) was obtained from Gibco; see *Proc. Soc. Exp.*

15 *Biol. Med.*, 1949, 71, 196.

Synthetic cell culture medium, RPMI 1640 was obtained from Gibco; it contains inorganic salts [Ca(NO<sub>3</sub>)<sub>2</sub>.4H<sub>2</sub>O 100 mg/l; KCl 400 mg/l; MgSO<sub>4</sub>.7H<sub>2</sub>O 100 mg/l; NaCl 6000 mg/l; NaHCO<sub>3</sub> 2000 mg/l & Na<sub>2</sub>HPO<sub>4</sub> (anhyd) 800 mg/l], D-Glucose 2000 mg/l, reduced glutathione 1 mg/l, amino acids and vitamins.

20 FURA-2/AM is 1-[2-(5-carboxyoxazol-2-yl)-6-aminobenzofuran-5-oxy]-2-(2'-amino-5'-methylphenoxy)-ethane-*N,N,N',N'*-tetraacetic acid pentaacetoxymethyl ester and was obtained from Molecular Probes, Eugene, Oregon, USA.

Blood Sedimentation Buffer contains 8.5g/l NaCl and 10g/l hydroxyethyl cellulose.

Lysis Buffer is 0.15M NH<sub>4</sub>Cl, 10mM KHCO<sub>3</sub>, 1mM EDTA

Whole Cell Binding Buffer is 50 mM HEPES, 1 mM CaCl<sub>2</sub>, 5 mM MgCl<sub>2</sub>, 0.5% BSA, 0.01% NaN<sub>3</sub>, adjusted to pH 7.2 with 1M NaOH.

Wash buffer is 50mM HEPES, 1mM CaCl<sub>2</sub>, 5mM MgCl<sub>2</sub>, 0.5% heat inactivated FCS, 0.5MNaCl adjusted to pH7.2 with 1M NaOH.

5 General molecular biology procedures can be followed from any of the methods described in "Molecular Cloning - A Laboratory Manual" Second Edition, Sambrook, Fritsch and Maniatis (Cold Spring Harbor Laboratory, 1989).

i) Cloning and expression of hMCP-1 receptor

The MCP-1 receptor B (CCR2B) cDNA was cloned by PCR from THP-1 cell RNA 10 using suitable oligonucleotide primers based on the published MCP-1 receptor sequences (Charo *et al.*, 1994, *Proc. Natl. Acad. Sci. USA*, **91**, 2752). The resulting PCR products were cloned into vector PCR-II™ (InVitrogen, San Diego, CA.). Error free CCR2B cDNA was subcloned as a Hind III-Not I fragment into the eukaryotic expression vector pCDNA3 (InVitrogen) to generate pCDNA3/CC-CKR2A and pCDNA3/CCR2B respectively.

15 Linearised pCDNA3/CCR2B DNA was transfected into CHO-K1 cells by calcium phosphate precipitation (Wigler *et al.*, 1979, *Cell*, **16**, 777). Transfected cells were selected by the addition of Geneticin Sulphate (G418, Gibco BRL) at 1mg/ml, 24 hours after the cells had been transfected. Preparation of RNA and Northern blotting were carried out as described previously (Needham *et al.*, 1995, *Prot. Express. Purif.*, **6**, 134). CHO-K1 clone 7 20 (CHO-CCR2B) was identified as the highest MCP-1 receptor B expressor.

ii) Preparation of membrane fragments

CHO-CCR2B cells were grown in DMEM supplemented with 10% foetal calf serum, 2 mM glutamine, 1x Non-Essential Amino Acids, 1x Hypoxanthine and Thymidine Supplement and Penicillin-Streptomycin (at 50 µg streptomycin/ml, Gibco BRL). Membrane 25 fragments were prepared using cell lysis/differential centrifugation methods as described previously (Siciliano *et al.*, 1990, *J. Biol. Chem.*, **265**, 19658). Protein concentration was estimated by BCA protein assay (Pierce, Rockford, Illinois) according to the manufacturer's instructions.

iii) Assay

30 <sup>125</sup>I MCP-1 was prepared using Bolton and Hunter conjugation (Bolton *et al.*, 1973, *Biochem. J.*, **133**, 529; Amersham International plc]. Equilibrium binding assays were carried out using the method of Ernst *et al.*, 1994, *J. Immunol.*, **152**, 3541. Briefly, varying amounts

of  $^{125}\text{I}$ -labeled MCP-1 were added to 7 $\mu\text{g}$  of purified CHO-CCR2B cell membranes in 100  $\mu\text{l}$  of Binding Buffer. After 1 hour incubation at room temperature the binding reaction mixtures were filtered and washed 5 times through a plate washer (Brandel MLR-96T Cell Harvester) using ice cold Binding Buffer. Filter mats (Brandel GF/B) were pre-soaked for 60 minutes in 5 0.3% polyethylenimine prior to use. Following filtration individual filters were separated into 3.5ml tubes (Sarstedt No. 55.484) and bound  $^{125}\text{I}$ -labeled MCP-1 was determined (LKB 1277 Gammamaster). Cold competition studies were performed as above using 100 pM  $^{125}\text{I}$ -labeled MCP-1 in the presence of varying concentrations of unlabelled MCP-1. Non-specific binding was determined by the inclusion of a 200-fold molar excess of unlabelled MCP-1 in the 10 reaction.

Ligand binding studies with membrane fragments prepared from CHO-CCR2B cells showed that the CCR2B receptor was present at a concentration of 0.2 pmoles/mg of membrane protein and bound MCP-1 selectively and with high affinity ( $\text{IC}_{50} = 110 \text{ pM}$ ,  $K_d = 120 \text{ pM}$ ). Binding to these membranes was completely reversible and reached equilibrium 15 after 45 minutes at room temperature, and there was a linear relationship between MCP-1 binding and CHO-CCR2B cell membrane concentration when using MCP-1 at concentrations between 100 pM and 500 pM.

Test compounds dissolved in DMSO (5 $\mu\text{l}$ ) were tested in competition with 100 pM labelled MCP-1 over a concentration range (0.01-50 $\mu\text{M}$ ) in duplicate using eight point 20 dose-response curves and  $\text{IC}_{50}$  concentrations were calculated.

Compounds tested of the present invention had  $\text{IC}_{50}$  values of 50 $\mu\text{M}$  or less in the hMCP-1 receptor binding assay described herein. For example Compound 81 had an  $\text{IC}_{50}$  of 6.86 $\mu\text{M}$ .

#### b) MCP-1 mediated calcium flux in THP-1 cells

25 The human monocytic cell line THP-1 was grown in a synthetic cell culture medium RPMI 1640 supplemented with 10 % foetal calf serum, 6mM glutamine and Penicillin-Streptomycin (at 50  $\mu\text{g}$  streptomycin/ml, Gibco BRL). THP-1 cells were washed in HBSS (lacking  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$ ) + 1 mg/ml BSA and resuspended in the same buffer at a density of  $3 \times 10^6$  cells/ml. The cells were then loaded with 1mM FURA-2/AM for 30 min at 30  $37^\circ\text{C}$ , washed twice in HBSS, and resuspended at  $1 \times 10^6$  cells/ml. THP-1 cell suspension (0.9 ml) was added to a 5 ml disposable cuvette containing a magnetic stirrer bar and 2.1 ml of prewarmed ( $37^\circ\text{C}$ ) HBSS containing 1 mg/ml BSA, 1 mM  $\text{MgCl}_2$  and 2 mM  $\text{CaCl}_2$ . The

cuvette was placed in a fluorescence spectrophotometer (Perkin Elmer, Norwalk, CT) and preincubated for 4 min at 37°C with stirring. Fluorescence was recorded over 70 sec and cells were stimulated by addition of hMCP-1 to the cuvette after 10 sec.  $[Ca^{2+}]_i$  was measured by excitation at 340 nm and 380 nm alternately and subsequent measurement of the intensity of 5 the fluorescence emission at 510 nm. The ratio of the intensities of the emitted fluorescent light following excitation at 340 nm and 380 nm, (R), was calculated and displayed to give and estimate of cytoplasmic  $[Ca^{2+}]$  according to the equation:-

$$[Ca^{2+}]_i = K_d \frac{(R - R_{min})}{(R_{max} - R)} (Sf2/Sb2)$$

10 where the  $K_d$  for FURA-2  $Ca^{2+}$  complex at 37°C was taken to be 224nm.  $R_{max}$  is the maximal fluorescence ratio determined after addition of 10 mM Ionomycin,  $R_{min}$  is the minimal ratio determined by the subsequent addition of a  $Ca^{2+}$  free solution containing 5 mM EGTA, and Sf2/Sb2 is the ratio of fluorescence values at 380 nm excitation determined at  $R_{min}$  and  $R_{max}$ , respectively.

15 Stimulation of THP-1 cells with hMCP-1 induced a rapid, transient rise in  $[Ca^{2+}]_i$  in a specific and dose dependent manner. Dose response curves indicated an approximate  $EC_{50}$  of 2 nm. Test compounds dissolved in DMSO (10 $\mu$ l) were assayed for inhibition of calcium release by adding them to the cell suspension 10 sec prior to ligand addition and measuring the reduction in the transient rise in  $[Ca^{2+}]_i$ . Test compounds were also checked for lack of 20 agonist activity by addition in place of hMCP-1.

**c) hMCP-1 and RANTES mediated chemotaxis.**

*In vitro* chemotaxis assays were performed using the human monocytic cell line THP-1. Cell migration through polycarbonate membranes was measured by enumerating those passing through either directly by Coulter counting or indirectly by use of a 25 colourimetric viability assay measuring the cleavage of a tetrazolium salt by the mitochondrial respiratory chain (Scudiero D.A. *et al.* 1988, *Cancer Res.*, **48**, 4827-4833).

Chemoattractants were introduced into a 96-well microtitre plate which forms the lower well of a chemotaxis chamber fitted with a PVP-free 5  $\mu$ m poresize polycarbonate adhesive framed filter membrane (NeuroProbe MB series, Cabin John, MD 20818, USA) 30 according to the manufacturer's instructions. The chemoattractant was diluted as appropriate in synthetic cell culture medium, RPMI 1640 (Gibco) or supplemented with 2 mM glutamine and 0.5% BSA, or alternatively with HBSS with  $Ca^{2+}$  and  $Mg^{2+}$  without Phenol Red (Gibco)

plus 0.1% BSA. Each dilution was degassed under vacuum for 30 min and was placed (400  $\mu$ l) in the lower wells of the chamber and THP-1 cells ( $5 \times 10^5$  in 100  $\mu$ l RPMI 1640 + 0.5% BSA) were incubated in each well of the upper chamber. For the inhibition of chemotaxis the chemoattractant was kept at a constant submaximal concentration determined 5 previously (1nM MCP-1) and added to the lower well together with the test compounds dissolved in DMSO (final DMSO concentration < 0.05% v/v) at varying concentrations. The chamber was incubated for 2 h at 37°C under 5 % CO<sub>2</sub>. The medium was removed from the upper wells which were then washed out with 200  $\mu$ l physiological saline before opening the chamber, wiping dry the membrane surface and centrifuging the 96-well plate at 600 g for 10 5 min to harvest the cells. Supernatant (150  $\mu$ l) was aspirated and 10  $\mu$ l of cell proliferation reagent, WST-1, {4-[3-(4-iodophenyl)-2-(4-nitrophenyl)-2H-5-tetrazolio]-1,3-phenyl 15 disulfonate} plus an electron coupling reagent (Boehringer Mannheim, Cat.no. 1644 807) was added back to the wells. The plate was incubated at 37°C for 3 h and the absorbance of the soluble formazan product was read on a microtitre plate reader at 450 nm. The data was input into a spreadsheet, corrected for any random migration in the absence of chemoattractant and the average absorbance values, standard error of the mean, and significance tests were calculated. hMCP-1 induced concentration dependent cell migration with a characteristic 20 biphasic response, maximal 0.5-1.0 nm.

In an alternative form of the above assay, fluorescently tagged cells can be used in 20 order to assist in end point detection. In this case, the THP-1 cells used are fluorescently tagged by incubation in the presence of 5mM Calcein AM (Glycine, N,N'-[[3',6'- bis(acetyloxy)-3-oxospiro[isobenzofuran-1(3H),9'-[9H]xanthene]-2',7'-diyl]bis(methylene)] bis[N-[2-[(acetyloxy)methoxy]-2-oxoethyl]]-bis[(acetyloxy)methyl] ester; Molecular Probes) 25 for 45 minutes in the dark. Cells are harvested by centrifugation and resuspended in HBSS (without Phenol Red) with Ca<sup>2+</sup>, Mg<sup>2+</sup> and 0.1% BSA. 50 $\mu$ l (2x10<sup>5</sup> cells) of the cell suspension are placed on the filter above each well and, as above, the unit is incubated at 37°C for 2 hours under 5% CO<sub>2</sub>. At the end of the incubation, cells are washed off the upper face of the filter with phosphate buffered saline, the filter removed from the plate and the number of 30 cells attracted to either the underside of the filter or the lower well estimated by reading fluorescence at 485nm excitation, 538nm emission wavelengths (fmax, Molecular Devices). The data was input into a spreadsheet, corrected for any random migration in the absence of chemoattractant and the average fluorescence values, standard error of the mean, percentage

inhibition and  $IC_{50}$  of compounds under test and significance tests can be calculated. In addition to MCP-1 induced chemotaxis, this alternative form of the assay was also used to measure inhibition of RANTES (2nM) induced chemotaxis.

**d) Binding to human peripheral blood mononuclear cells(PBMCs)**

5 i) Preparation of human PBMCs

Fresh human blood (200ml) was obtained from volunteer donors, collected into sodium citrate anticoagulant to give a final concentration of 0.38%. The blood was mixed with Sedimentation Buffer and incubated at 37°C for 20 minutes. The supernatant was collected and centrifuged at 1700rpm for 5 minutes (Sorvall RT6000D). The pellet obtained 10 was resuspended in 20 ml RPMI/BSA (1mg/ml) and 4 x 5mls of cells were carefully layered over 4 x 5mls of Lymphoprepä (Nycomed) in 15ml centrifuge tubes. Tubes were spun at 1700rpm for 30 minutes (Sorvall RT6000D) and the resultant layer of cells was removed and transferred to 50ml Falcon tubes. The cells were washed twice in Lysis Buffer to remove any 15 remaining red blood cells followed by 2 washes in RPMI/BSA. Cells were resuspended in 5mls of Binding Buffer. Cell number was measured on a Coulter counter and additional binding buffer was added to give a final concentration of  $1.25 \times 10^7$  PBMCs /ml.

ii) Assay

[ $^{125}$ I]MCP-1 was prepared using Bolton and Hunter conjugation (Bolton *et al.*, 1973, *Biochem. J.*, **133**, 529; Amersham International plc]. Equilibrium binding assays were carried 20 out using the method of Ernst *et al.*, 1994, *J. Immunol.*, **152**, 3541. Briefly, 50 $\mu$ l of  $^{125}$ I-labeled MCP-1 (final concentration 100pM) was added to 40 $\mu$ l ( $5 \times 10^5$  cells) of cell suspension in a 96 well plate. Compounds, diluted in Whole Cell Binding Buffer from a stock solution of 10mM in DMSO were added in a final volume of 5 $\mu$ l to maintain a constant DMSO concentration in the assay of 5%. Total binding was determined in the absence of compound. Non-specific 25 binding was defined by the addition of 5 $\mu$ l cold MCP-1 to give a final assay concentration of 100nM. Assay wells were made up to a final volume of 100 $\mu$ l with Whole Cell Binding Buffer and the plates sealed. Following incubation at 37°C for 60 minutes the binding reaction mixtures were filtered and washed for 10 seconds using ice cold Wash Buffer using a plate washer (Brandel MLR-96T Cell Harvester). Filter mats (Brandel GF/B) were pre-soaked for 30 60 minutes in 0.3% polyethylenimine plus 0.2% BSA prior to use. Following filtration individual filters were separated into 3.5ml tubes (Sarstedt No. 55.484) and bound  $^{125}$ I-labeled MCP-1 was determined (LKB 1277 Gammamaster).

Test compound potency was determined by assay in duplicate using six point dose-response curves and IC<sub>50</sub> concentrations were determined.

For example, using this method, compound No. 14 in Table I showed an IC<sub>50</sub> of 11.4μM in the hMCP-1 chemotaxis assay and compound No.23 in Table 1 showed an IC<sub>50</sub> of 2.95μM in the RANTES chemotaxis assay.

No physiologically unacceptable toxicity was observed at the effective dose for compounds tested of the present invention.

### Example 33

#### Pharmaceutical Compositions

10 The following Example illustrates, but is not intended to limit, pharmaceutical dosage forms of the invention as defined herein (the active ingredient being termed "Compound X"), for therapeutic or prophylactic use in humans:

(a)

<u>Tablet I</u>	<u>mg/tablet</u>
Compound X.	100
Lactose Ph.Eur	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v paste)	2.25
Magnesium stearate	3.0

15

(b)

<u>Tablet II</u>	<u>mg/tablet</u>
Compound X	50
Lactose Ph.Eur	223.75
Croscarmellose sodium	6.0
Maize starch	15.0
Polyvinylpyrrolidone (5% w/v paste)	2.25
Magnesium stearate	3.0

(c)

<u>Tablet III</u>	<u>mg/tablet</u>
Compound X	1.0
Lactose Ph.Eur	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v paste)	0.75
Magnesium stearate	1.0

(d)

<u>Capsule</u>	<u>mg/capsule</u>
Compound X	10
Lactose Ph.Eur	488.5
Magnesium	1.5

5

(e)

<u>Injection I</u>	<u>(50 mg/ml)</u>
Compound X	5.0% w/v
1M Sodium hydroxide solution	15.0% v/v
0.1M Hydrochloric acid	to adjust pH to 7.6
Polyethylene glycol 400	4.5% w/v
Water for injection	to 100%

(f)

<u>Injection II</u>	<u>(10 mg/ml)</u>
Compound X	1.0% w/v
Sodium phosphate BP	3.6% w/v
0.1M Sodium hydroxide solution	15.0% v/v
Water for injection	to 100%

(g)

<u>Injection III</u>	(1mg/ml, buffered to pH6)
Compound X	0.1% w/v
Sodium phosphate BP	2.26% w/v
Citric acid	0.38% w/v
Polyethylene glycol 400	3.5% w/v
Water for injection	to 100%

(h)

<u>Aerosol I</u>	<u>mg/ml</u>
Compound X	10.0
Sorbitan trioleate	13.5
Trichlorofluoromethane	910.0
Dichlorodifluoromethane	490.0

5 (i)

<u>Aerosol II</u>	<u>mg/ml</u>
Compound X	0.2
Sorbitan trioleate	0.27
Trichlorofluoromethane	70.0
Dichlorodifluoromethane	280.0
Dichlorotetrafluoroethane	1094.0

(j)

<u>Aerosol III</u>	<u>mg/ml</u>
Compound X	2.5
Sorbitan trioleate	3.38
Trichlorofluoromethane	67.5
Dichlorodifluoromethane	1086.0
Dichlorotetrafluoroethane	191.6

(k)

<u>Aerosol IV</u>	<u>mg/ml</u>
Compound X	2.5
Soya lecithin	2.7
Trichlorofluoromethane	67.5
Dichlorodifluoromethane	1086.0
Dichlorotetrafluoroethane	191.6

(l)

<u>Ointment</u>	<u>ml</u>
Compound X	40 mg
Ethanol	300 µl
Water	300 µl
1-Dodecylazacycloheptan-2-one	50 µl
Propylene glycol	to 1 ml

5 Note:

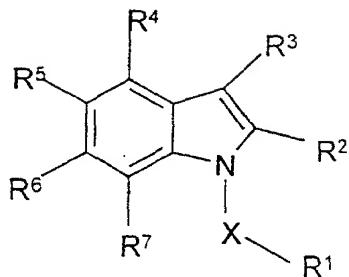
Compound X in the above formulation may comprise a compound illustrated in Examples herein. The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate. The aerosol

10 formulations (h)-(k) may be used in conjunction with standard, metered dose aerosol dispensers, and the suspending agents sorbitan trioleate and soya lecithin may be replaced by an alternative suspending agent such as sorbitan monooleate, sorbitan sesquioleate, polysorbate 80, polyglycerol oleate or oleic acid.

Claims

1. The use of a compound of formula (I)

5



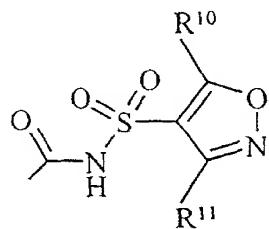
(I)

or a pharmaceutically acceptable salt, amide or ester thereof;

10 X is  $\text{CH}_2$  or  $\text{SO}_2$

$\text{R}^1$  is an optionally substituted aryl or heteroaryl ring;

$\text{R}^2$  is carboxy, cyano,  $-\text{C}(\text{O})\text{CH}_2\text{OH}$ ,  $-\text{CONHR}^8$ ,  $-\text{SO}_2\text{NHR}^9$ , tetrazol-5-yl,  $\text{SO}_3\text{H}$ , or a group of formula (VI)



15

(VI)

where  $\text{R}^8$  is selected from hydrogen, alkyl, aryl, cyano, hydroxy,  $-\text{SO}_2\text{R}^{12}$  where  $\text{R}^{12}$  is alkyl, aryl, heteroaryl, or haloalkyl, or  $\text{R}^8$  is a group- $(\text{CHR}^{13})_r\text{-COOH}$  where  $r$  is an integer of 1-3 and each  $\text{R}^{13}$  group is independently selected from hydrogen or alkyl;  $\text{R}^9$  is hydrogen, alkyl, optionally substituted aryl such as optionally substituted phenyl or optionally substituted

20 heteroaryl such as 5 or 6 membered heteroaryl groups, or a group  $\text{COR}^{14}$  where  $\text{R}^{14}$  is alkyl, aryl, heteroaryl or haloalkyl;  $\text{R}^{10}$  and  $\text{R}^{11}$  are independently selected from hydrogen or alkyl, particularly  $\text{C}_{1-4}$  alkyl;

R<sup>3</sup> is a group OR<sup>15</sup>, S(O)<sub>q</sub>R<sup>15</sup>, NHCOR<sup>16</sup>, NHSO<sub>2</sub>R<sup>16</sup>, (CH<sub>2</sub>)<sub>s</sub>COOH, (CH<sub>2</sub>)<sub>t</sub>CONR<sup>17</sup>R<sup>18</sup>, NR<sup>17</sup>R<sup>18</sup>, SO<sub>2</sub>NR<sup>17</sup>R<sup>18</sup> or optionally substituted alkenyl, where q is 0, 1 or 2, s is 0 or an integer of from 1 to 4, t is 0 or an integer of from 1 to 4, R<sup>15</sup> is a substituted alkyl or cycloalkyl group or an optionally substituted heteroaryl group, R<sup>16</sup> is optionally substituted alkyl,

5 optionally substituted aryl or optionally substituted heteroaryl and R<sup>17</sup> and R<sup>18</sup> are independently selected from hydrogen, optionally substituted alkyl, optionally substituted aryl and optionally substituted heteroaryl, with the proviso that at least one of R<sup>17</sup> or R<sup>18</sup> is other than hydrogen, or R<sup>16</sup> and R<sup>17</sup> together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring which optionally contains further

10 heteroatoms; and

R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are independently selected from hydrogen, a functional group or an optionally substituted hydrocarbyl groups or optionally substituted heterocyclic groups, provided that R<sup>4</sup> is other than a group, OR<sup>18</sup>, S(O)<sub>m</sub>R<sup>18</sup>, NR<sup>19</sup>R<sup>20</sup>, C(O)NR<sup>19</sup>R<sup>20</sup>, NHCOR<sup>18</sup>, NHSO<sub>2</sub>R<sup>18</sup> or OCONR<sup>19</sup>R<sup>20</sup> or an alkyl group substituted by OR<sup>18</sup>, S(O)<sub>m</sub>R<sup>18</sup>, NR<sup>19</sup>R<sup>20</sup> where R<sup>18</sup>

15 , R<sup>19</sup> and R<sup>20</sup> are independently selected from hydrogen or optionally substituted hydrocarbyl, or R<sup>19</sup> and R<sup>20</sup> together with the atom to which they are attached, form an optionally substituted heterocyclic ring as defined above which optionally contains further heteroatoms such as S(O)<sub>n</sub>, oxygen and nitrogen, m is 0 or an integer of 1-3 and R<sup>18</sup> is a substituted hydrogen-containing alkyl group,

20 for use in the preparation of a medicament for the inhibition of monocyte chemoattractant protein-1 and/or RANTES induced chemotaxis.

2. The use according to claim 1 wherein in the compound of formula (I), R<sup>4</sup> is hydrogen, hydroxy, halo, alkoxy, aryloxy or an optionally substituted hydrocarbyl group or optionally substituted heterocyclic group.

3. The use according to any one of the preceding claims Particular groups R<sup>1</sup> include OR<sup>15</sup>, S(O)<sub>q</sub>R<sup>15</sup>, NHCOR<sup>16</sup>, NHSO<sub>2</sub>R<sup>16</sup>, SO<sub>2</sub>NR<sup>17</sup>R<sup>18</sup> where q, R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup> and R<sup>18</sup> are as defined in claim 1.

4. The use according to any one of the preceding claims wherein R<sup>3</sup> is a group of formula -O(CH<sub>2</sub>)<sub>a</sub>[(CHOH)(CH<sub>2</sub>)<sub>b</sub>]<sub>d</sub>CH<sub>2</sub>OH where a is 0 or an integer of from 1 to 4, b is 0 or an integer of from 1 to 3, and d is 0, or 1.

5 5. The use according to any one of the preceding claims wherein R<sup>1</sup> is 3,4-dichlorophenyl, 3-fluoro-4-chlorophenyl, 3-chloro-4-fluorophenyl or 2,3-dichloropyrid-5-yl.

6. The use according to any one of the preceding claims where X is CH<sub>2</sub>.

10 7. A compound for use in therapy, said compound comprising a compound of formula (1A) which is a compound of formula (I) as defined in claim 1 subject to the following provisos:

(i) when R<sup>2</sup> is carboxy or a salt or amide thereof, at least three of R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are hydrogen, and R<sup>3</sup> is S(O)qR<sup>15</sup>, R<sup>15</sup> is other than C<sub>1-4</sub> alkyl substituted by carboxy or an ester or amide derivative thereof;

(ii) when R<sup>3</sup> is a group NHCOR<sup>16</sup> or NHSO<sub>2</sub>R<sup>16</sup>, R<sup>16</sup> is optionally substituted alkyl; and

(iii) where R<sup>3</sup> is a group SR<sup>14</sup> where R<sup>14</sup> is 2-quinolylmethyl, R<sup>2</sup> is COOH or an ethyl ester thereof, each of R<sup>4</sup>, R<sup>5</sup>, and R<sup>7</sup> are hydrogen, R<sup>1</sup> is 4-chlorophenyl, R<sup>6</sup> is other than 2-quinolylmethyl.

20

8. A pharmaceutical compositions comprising a compound of formula (1A) as defined in claim 7 in combination with a pharmaceutically acceptable carrier.

9. A compound of formula (1B) which is a compound of formula (1A) as defined in claim 7, subject to the following further provisos:

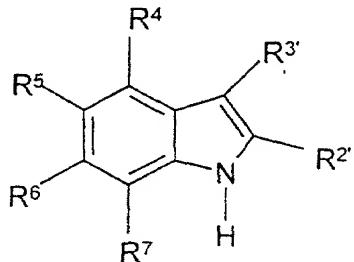
(iv) where R<sup>3</sup> is a group COOH or CH<sub>2</sub>COOH, R<sup>2</sup> is COOH and each of R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are hydrogen, R<sup>1</sup> is other than unsubstituted phenyl; and

(v) where R<sup>3</sup> is a group CH<sub>2</sub>COOH, R<sup>2</sup> is COOH and each of R<sup>4</sup>, R<sup>5</sup>, and R<sup>7</sup> are hydrogen, R<sup>1</sup> is 4-chlorophenyl, R<sup>6</sup> is other than methoxy; and

30 (vi) when R<sup>3</sup> is OR<sup>15</sup> or S(O)<sub>q</sub>R<sup>15</sup>, R<sup>15</sup> is other than C<sub>1-6</sub> haloalkyl; and

(vii) when R<sup>2</sup> is COOCH<sub>2</sub>CH<sub>3</sub>, each of R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are hydrogen, and R<sup>1</sup> is 4-chlorophenyl, then R<sup>3</sup> is other than a group CH=CH(CN)<sub>2</sub>.

10. A method of preparing a compound of formula (I) as defined in claim 1, which method comprises reacting a compound of formula (VII)



5

(VII)

where R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are as defined in relation to formula (I), R<sup>2'</sup> is a group R<sup>2</sup> as defined in relation to formula (I) or a protected form thereof, and R<sup>3'</sup> is a group R<sup>3</sup> as defined in relation to formula (I) or a precursor thereof; with compound of formula (VIII)

10

R<sup>1</sup>-X-Z<sup>1</sup>

(VIII)

where R<sup>1</sup> and X are as defined in relation to formula (I) and Z<sup>1</sup> is a leaving group; and thereafter if desired or necessary carrying out one or more of the following steps:

15 (i) changing a precursor group R<sup>3'</sup> to a group R<sup>3</sup> or a group R<sup>3</sup> to a different such group;  
(ii) removing any protecting group from R<sup>2'</sup>.

FOR UTILITY/DESIGN  
CIP/IPC NATIONAL PLANT  
ORIGINAL/SUBSTITUTE/SUPPLEMENTAL  
DECLARATIONS

RULE 63 (37 C.F.R. 1.63)  
DECLARATION AND POWER OF ATTORNEY  
FOR PATENT APPLICATION  
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PW  
FORM  
Z 70470/UST

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name, and I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the INVENTION ENTITLED INDOLE DERIVATIVES AS ANTI-INFLAMMATION AGENTS

the specification of which (CHECK applicable BOX(ES))  
X  is attached hereto  
BOX(ES)  B.  was filed on \_\_\_\_\_ as U.S. Application No. \_\_\_\_\_

C.  was filed as PCT International Application No. PCT/GB00/00284 on 31 January 2000  
and (if applicable to U.S. or PCT application) was amended on \_\_\_\_\_ I hereby state that I have reviewed and understand the contents of the above identified specification including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. 1.56. Except as noted below, I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate or 365(a) of any PCT International Application which designated at least one other country than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate, or PCT International Application, filed by me or my assignee disclosing the subject matter claimed in this application and having a filing date (1) before that of the application on which priority is claimed or (2) if no priority claimed, before the filing date of this application.

PRIOR FOREIGN APPLICATION(S) Number	Country	Day/MONTH/Year Filed	Date first laid- open or Published	Date Patented or Granted	Priority NOT Claimed
9902455.6	United Kingdom	5 February 1999			

Except as noted below, I hereby claim domestic priority benefit under 35 U.S.C. 119(e) or 120 and/or 365(c) of the indicated United States applications listed below and PCT international applications listed above or below and, if this is a continuation-in-part (CIP) application, insofar as the subject matter disclosed and claimed in this application is in addition to that disclosed in such prior applications, I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. 1.56 which became available between the filing date of each such prior application and the national or PCT international filing date of this application.

PRIOR U.S. PROVISIONAL, NON PROVISIONAL AND/OR PCT APPLICATION(S) Application No. (series code/serial no.)	Day/MONTH/Year Filed	Status	Priority NOT Claimed
		Pending, abandoned, patented	

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

And I hereby appoint Pillsbury Winthrop LLP, Intellectual Property Group, telephone number (202)861-3000 (to whom all communications are to be directed), and persons of that firm who are associated with USPTO Customer No.909 (see below label) individually and collectively my attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith and with the resulting patent, and I hereby authorize them to delete from that Customer No. names of persons no longer with their firm, to add new persons of their firm to that Customer No., and to act and rely on instructions from and communicate directly with the person/assignee/attorney/firm/organization who/which first sends/sent this case to them and by whom/which I hereby declare that I have consented after full disclosure to be represented unless/until I instruct the above Firm and/or an attorney of that Firm in writing to the contrary.

00909

Date: 17<sup>th</sup> July 2001

(1) INVENTOR'S SIGNATURE *Alan Weller*

Name	ALAN	W	FAULL
	First	Middle Initial	Family Name
Residence	Macclesfield, Cheshire,	United Kingdom	GBX United Kingdom
	City	State/Foreign Country	Country of Citizenship
Mailing Address	Alderley Park, Macclesfield, Cheshire SK10 4TG, United Kingdom.		
(include Zip Code)			

(2) INVENTOR'S SIGNATURE

Date: 5 July 2001

Name	JASON	KETTLE
	First	Middle Initial
Residence	Macclesfield, Cheshire	United Kingdom
	City	State/Foreign Country
Mailing Address	Alderley Park, Macclesfield, Cheshire SK10 4TG, United Kingdom	
(include Zip Code)		

OR ADDITIONAL INVENTORS see attached page.

See additional foreign priorities on attached page (incorporated herein by reference).

Atty. Dkt. No. P

(M#)

#### DECLARATION AND POWER OF ATTORNEY

(continued)

Additional Inventors

Page 2

(3) INVENTOR'S SIGNATURE

Date: